

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2005/032821

International filing date: 14 September 2005 (14.09.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/610,038
Filing date: 14 September 2004 (14.09.2004)

Date of receipt at the International Bureau: 16 December 2005 (16.12.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

1401992

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 06, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 60/610,038

FILING DATE: *September 14, 2004*

RELATED PCT APPLICATION NUMBER: *PCT/US05/32821*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US60/610,038*



Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

PROVISIONAL APPLICATION COVER SHEET

Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

DOCKET NO.: M1015.70090US00
Express Mail Label No.: EV 292566483 US
Date of Deposit: September 14, 2004

17513 U.S. PTO
60/610038

INVENTOR(S)/APPLICANT(S)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Bamdad	Cynthia	C.	Boston, MA

☐ Additional inventors are being named on the separately numbered sheets attached hereto.

TITLE OF THE INVENTION (280 characters max)

TECHNIQUES FOR DIAGNOSIS AND TREATMENT OF CANCER (MUC 1)

CORRESPONDENCE ADDRESS

CUSTOMER NUMBER:
23628

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification - Number of Pages = 113 (91 pages of Specification; 22 pages of Claims)

☒ Application Data Sheet, See 37 CFR 1.76

☒ Return receipt postcard

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No

☐ Yes, the name of the U.S., Government Agency and the Government Contract Number are:

☐ Other:

METHOD OF PAYMENT (check all that apply)

☐ A check is enclosed to cover the Provisional Filing Fees.

☒ The Commissioner is hereby authorized to charge any additional fees or credit overpayment to Deposit Account 23/2825. A duplicate of this sheet is enclosed.

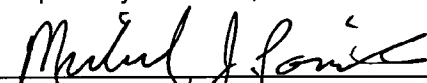
☐ Small Entity Status is claimed.

PROVISIONAL FILING FEE AMOUNT \$ 160.00

September 14, 2004

Date

Respectfully submitted,


Michael J. Pomianek, Reg. No. 46,190
Telephone No.: 617-646-8000

TECHNIQUES FOR DIAGNOSIS AND TREATMENT OF CANCER (MUC 1)

Related Applications

The following patent applications and publications may disclose subject matter
5 related to the subject matter disclosed below: U.S. Patent Application Serial No.
10/237,150, now published as Publication No. U.S. 2003/0130293 A1; which claims
the benefit under Title 35, U.S.C. §119(e) of U.S. Provisional Patent Application No.
60/317,302 and U.S. Provisional Patent Application No. 60/376,732.; International
Patent Application No. (not yet assigned), filed August 26, 2004 bearing attorney
10 docket no. M1015.70089WO00, entitled "TECHNIQUES AND COMPOSITIONS
FOR THE DIAGNOSIS AND TREATMENT OF CANCER (MUC1)" by C. Bamdad;
which claims the benefit under Title 35, U.S.C. §119(e) of U.S. Provisional Patent
Application No. 60/498,260; and which is a continuation-in-part of U.S. Patent
Application Serial No. 09/996,069, now published as Publication No. U.S.
15 2003/0036199 A1; which claims the benefit under Title 35, U.S.C. §119(e) of U.S.
Provisional Patent Application Nos. 60/253,361; 60/256,027; 60/258,157; 60/259,615;
60/260,186; 60/266,169; 60/289,444; 60/266,929; 60/278,093; 60/294,887; and
60/298,272. Each of these applications and publications is incorporated herein by
reference.

20

Field of the Invention

This invention generally relates to methods and compositions for the diagnosis
and treatment of cancers that are characterized by the presence of the MUC1 receptor
and, in particular, to cancers that are characterized by the aberrant expression of the
25 MUC1 receptor. The invention also can relate to methods for diagnosing and tracking
a patient's response to therapy for MUC1-positive cancers.

Description of the Related Art

As our knowledge of cancer grows, it has become increasingly clear that cancer
is not a single disease, but rather a collection of diseases that share some common
30 characteristics. Indeed, both the treatment and the characterization of cancers are

changing rapidly as causative factors are identified at the molecular level and molecular “signatures” of sub-types of cancer are discovered. The treatment of breast cancers is being increasingly designed to target specific molecular signatures that are present in that particular cancer and in that particular patient. Excised breast tumors are often
5 tested to determine whether they present, or present elevated levels, of estrogen receptor, progesterone-receptor, or more recently the Her2/neu receptor. The characterization of tumors at the molecular level guides the physician in the choice of possible treatments for a particular patient. Therapies that are molecularly tuned to a particular patient have had a measurable impact of cancer recurrence and survival. For
10 example, patients with estrogen-receptor positive (ER+) and/or progesterone-receptor positive (PR+) cancers are typically treated with Tamoxifen for a period of up to 5 years. Tamoxifen, an estrogen analog, works by binding to and blocking the estrogen receptor's natural estrogen docking site. The recurrence rate of the cancer is dependent on several factors, but in general, patients with cancers that are both ER+ and PR+ fare
15 better (efficacy ~70%) than those that are either ER+ *or* PR+ (efficacy ~30%), or ER-/PR- (efficacy ~10%). Herceptin is an antibody-based therapeutic that binds to and blocks Her2/neu receptor and has been shown to be effective against tumors that over-express this receptor. Gleevec® is a drug that treats chronic myeloid leukemia (CML). The drug inhibits the tyrosine kinase BCR-ABL, which is constitutively active in this
20 type of cancer cell and initiates a cell growth signal. Blocking BCR-ABL and intercepting the growth signal halts proliferation; the lack of cell proliferation then induces the programmed cell death called apoptosis. Because this drug works on a target molecule that is aberrant in cancer cells, it has a very high cure rate and few if any side effects. Unfortunately, the mechanism that goes awry in CML represents only
25 a small percentage of human cancers.

However, these results demonstrate that therapies that target specific molecules that are involved in the progression of cancer are more effective than earlier therapies that simply inhibit broad-spectrum cell growth. The new generation of cancer drugs such as herceptin and Gleevec and others being developed are called “smart” drugs
30 because they home in on and disable specific molecules that are involved in cancer, or more often a particular type of cancer. Thus, in order to effectively determine which

therapies are best for a particular patient, the patient's cancer can be characterized at the molecular level and treatments that act on specific aberrant molecules determined by the characterization can then be administered. Failure to characterize a cancer according to molecular signatures prior to treatment could cause the patient more harm than good. For example, by treating a patient with a drug that targets a particular molecule that is aberrant in some cancers, but not the type of cancer that the patient presents with, would constitute withholding appropriate treatment from that patient.

The MUC1 receptor is aberrantly expressed in a number of cancer types. MUC1 is a transmembrane glycoprotein found on the surface of epithelial cells. It has been reported that an estimated 75% of all human solid tumors aberrantly express the MUC1 receptor, including more than 90% of breast cancers and approximately 50% of prostate cancers. Other cancers in which the MUC1 receptor is aberrantly expressed include ovarian, colorectal, pancreatic, some lung cancers, and several others. For some time it has been known that in a healthy cell, the MUC1 receptors are clustered at the apical border, while in cancer cells, it appears to be uniformly expressed over the entire cell surface. This loss of clustering has been correlated to degree of cancer aggressiveness and patient prognosis. It is also known that the MUC1 receptor can be cleaved and shed from the cell surface. Shed receptor can be detected in the blood of healthy patients as well as breast cancer patients. Pregnant or lactating women have higher shed MUC1 levels in serum, while non-pregnant women, regardless of previous pregnancies, have present, but significantly lower levels in serum. Elevated levels of shed MUC1 are only present in small percentage of patients with localized disease (Stage I). As a general rule, MUC1 shedding occurs more frequently as the cancer increases in stage, becoming metastatic. Tests that assess the serum levels of shed MUC1 are approved by the FDA for the detection of breast cancer recurrence in patients initially diagnosed with Stage II or III breast cancer. These tests utilize an antibody that recognizes the terminal repeat units of the MUC1 receptor, which can vary from person to person even in the healthy state. This variability in the number of repeat units introduces variability into the test and thus limits its utility for tracking a patient's response to therapy and prevents its use as a diagnostic.

Proteases comprise another category of proteins that pharmaceutical companies are investigating as therapeutic targets. For example, protease inhibitors are effective treatments for HIV. Metalloproteases have been suggested as therapeutic targets of interest for a variety of conditions, including but not limited to cancers. Metzincins are a super-family of metalloproteins that includes three families of metalloproteases: MMPs, ADAMs, and ADAMTSs (ADAMs which contain one or more thrombospondin (TS) domains). These cleavage enzymes are produced as zymogens, which are not proteolytically active until a pro-peptide or pro-domain is cleaved or removed from its surface. This final processing step typically takes place at the cell surface. However, a subset of the metzincins are cleaved to generate the active enzyme in the golgi by furin or a furin-like enzyme. TIMPs (tissue inhibitors of metalloproteinases) are small proteins that bind to some metalloproteases and inhibit their proteolytic activity.

MMPs (matrix metalloproteinases) are a class of zinc-dependent endoproteases, wherein the metal is required for its activity. Six membrane-tethered MMPs, called MT-MMPs have been identified: MT1-MMP, MT2-MMP, MT3-MMP, MT4-MMP, MT5-MMP and MT6-MMP. All the MT-MMPs are processed to the proteolytically active form by furin. The MMPs were first named for their ability to degrade components of the extracellular matrix. Now, however, MMPs as well as other metalloproteases are emerging as a class of therapeutic targets for the treatment of inflammatory diseases and cancer. ADAM-17 is currently of pharmaceutical interest for the treatment of rheumatoid arthritis because it is required for the production of soluble TNF α .

Thus, there is a need to develop new and more accurate molecular signatures of cancers, develop diagnostic methods for characterizing cancers based on these signatures, and develop new therapeutic agents that act on those molecules that are specific to a type of cancer.

Summary of the Invention

Certain embodiments of the present invention relate to compositions that are able to inhibit MUC1-related proliferative diseases, particularly cancers, involving

inhibiting the portion of MUC1 that functions as a Growth Factor Receptor, cleavage of the full-length receptor to its tumorigenic form or interaction of the MUC1 receptor with its ligands, and methods for treating patients displaying symptoms of, or susceptible to MUC1-associated cancers by either inhibiting direct interactions or by
5 inhibiting their expression. The subject matter of this application involves, in some cases, interrelated products, alternative solutions to a particular problem, and/or a plurality of different uses of a single system or article.

Several methods are disclosed herein of administering to a subject a composition for prevention or treatment of a particular condition. It is to be understood
10 that in each such aspect of the invention, the invention specifically includes the composition for use in the treatment or prevention of that particular condition, as well as use of the composition for the manufacture of a medicament for the treatment or prevention of that particular condition. In some aspects of the invention, the invention also includes a pharmaceutically acceptable carrier.

15 The present invention includes methods of treatment of selected groups of patients. It is to be understood that all compositions described herein are useful or potentially useful for each described method.

Also included in certain embodiments of the present invention is a combinatorial approach in which structural features identified as characteristic of
20 compositions effective for treatment at various disease stages are used as the basis for combinatorial synthesis of a wide variety of structural homologs, analogs, derivatives, enantiomers and functionally equivalent compositions thereof, for identification of a wide variety of compositions useful for treatment MUC1-associated cancers. Thus, in one embodiment, the invention involves providing any one or more of compositions 1-
25 183, performing a combinatorial synthesis resulting in a plurality of compositions. Then, one can perform an assay involving the plurality of the compositions to determine their effectiveness in cancer treatment, specifically, for example, treatment of cancers disclosed herein. Compositions 1-183 also can be altered using medicinal chemistry techniques.

30 Another aspect of the invention provides, in certain embodiments, a pharmaceutical preparation comprising a composition comprising any of the

compositions 1-183, and a pharmaceutically active carrier. In one embodiment, compositions can comprise homologs, analogs, derivatives, enantiomers and functionally equivalent compositions thereof of compositions 1-183. In all structures herein, atom locations, if unlabeled, are carbon with appropriate hydrogen(s).

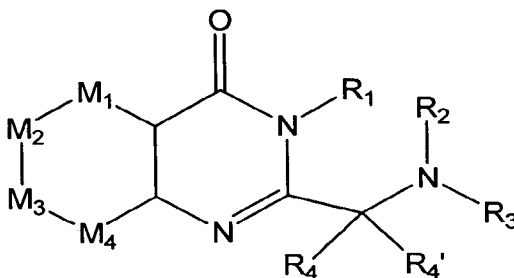
5 The invention also provides, in certain embodiments, a method involving promoting the prevention or treatment of MUC1-associated cancer via administration of any one or more of the compositions of the present invention and/or homologs, analogs, derivatives, enantiomers and functionally equivalent compositions thereof.

10 In another aspect the invention provides a kit including any one or more of the compositions of the present invention and/or homologs, analogs, derivatives, enantiomers and functionally equivalent compositions thereof; and instructions for use of these compositions for treatment of cancer characterized by aberrant expression of MUC1.

15 In one aspect, the invention is defined, at least in part, by a method. In some embodiments of the invention, the method involves treating a human patient susceptible to or exhibiting symptoms of a cancer characterized by aberrant expression of MUC1 with any of the compositions disclosed herein. In one set of embodiments, the patient is susceptible of, but does not exhibit symptoms of, cancer characterized by aberrant expression of MUC1. In another set of embodiments, the patient exhibits symptoms of
20 cancer characterized by aberrant expression of MUC1. In some embodiments of the method, the patient is not otherwise indicated for treatment for a cancer characterized by aberrant expression of a hedgehog protein.

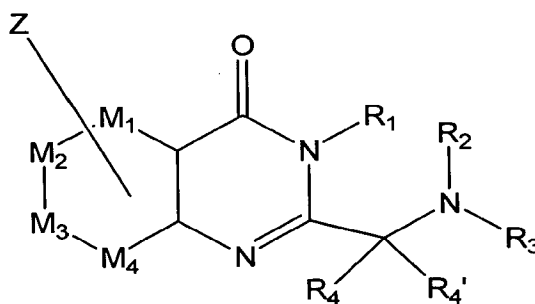
25 In another aspect, the invention is directed to a method of making any of the embodiments described herein. In yet another aspect, the invention is directed to a method of using any of the embodiments described herein.

 In one aspect, the invention involves a composition comprising compounds of a general structure and formula that can be routinely prepared by well-established methods. In one set of embodiments, the composition has a structure:



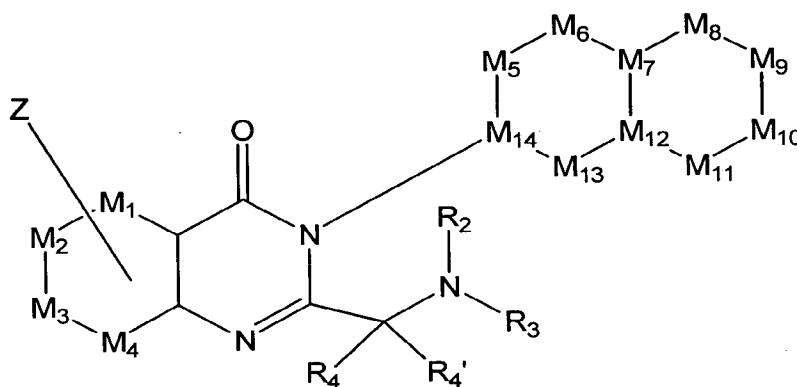
where M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction and chemical stability is achieved. Substitutions at positions $M_1 - M_4$ on the above atoms may be hydrogen or halogen, or an atomic null as required for valance satisfaction and chemical stability. R_1 is to be any atom other than halogen; R_2 and R_3 are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles. R_4 and R_4' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R_4 and R_4' may be covalently linked to give a set of cyclic compounds.

In another set of embodiments, the composition has a structure:



where M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction is achieved. Single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon and nitrogen atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or null as required for valance satisfaction and chemical stability. R_1 is to be any atom other than halogen. R_2 and R_3 are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles. R_4 and R_4' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R_4 and R_4' may be covalently linked to give a set of cyclic compounds.

In another set of embodiments, the composition has a structure:



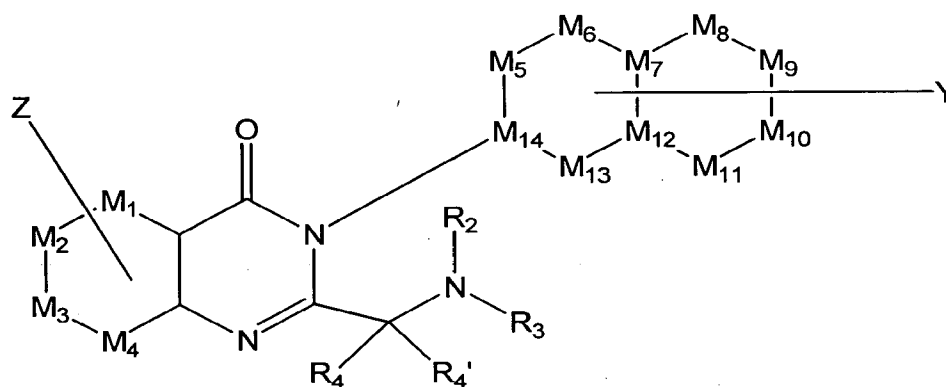
15

where M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction and chemical stability is achieved. Single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R_1 (M_5-M_{14}) is

20

to be any substituted atom other than hydrogen or halogen and, in certain embodiments, may be either a moiety where M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved. R₂ and R₃ are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R₂ and R₃ may be covalently linked to give a set of monocyclic *aza*-cycles. R₄ and R_{4'} may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R₄ and R_{4'} may be covalently linked to give a set of cyclic compounds.

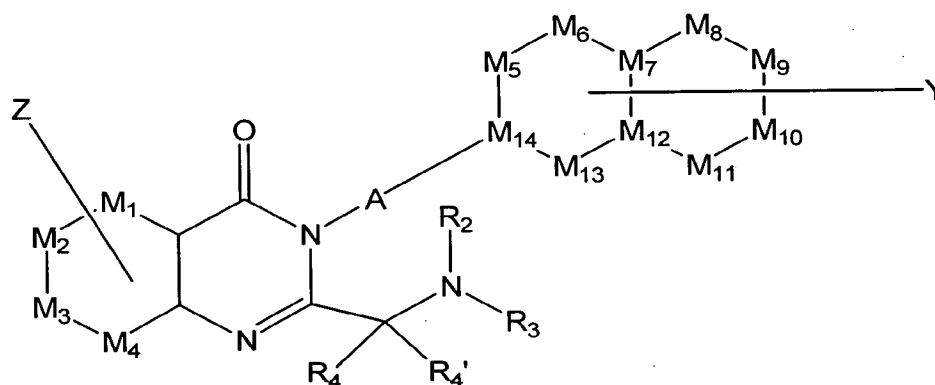
In another set of embodiments, the composition has a structure:



where M₁, M₂, M₃ and M₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction and chemical stability is achieved. Single and multiple substitutions by atom(s) Z at positions M₁ – M₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R₁ (M₅-M₁₄) is to be any substituted atom other than hydrogen or halogen and, in certain embodiments, may be either a moiety where M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are

each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R₂ and R₃ are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R₂ and R₃ may be covalently linked to give a set of monocyclic *aza*-cycles. R₄ and R₄' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R₄ and R₄' may be covalently linked to give a set of cyclic compounds

In another set of embodiments, the composition has a structure:



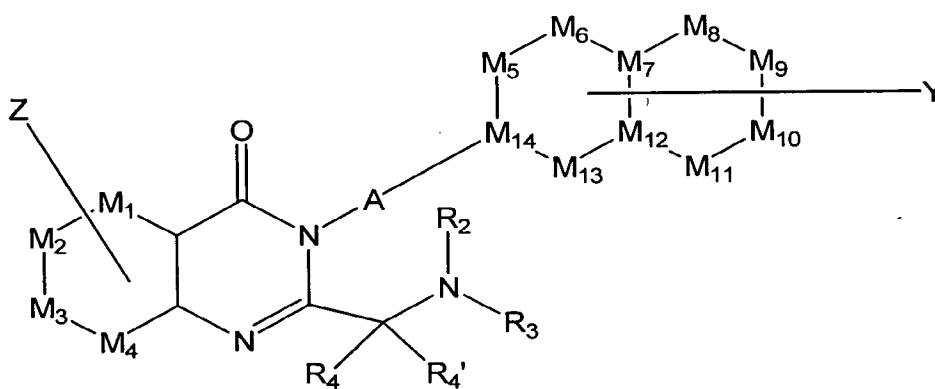
15

where M₁, M₂, M₃ and M₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction and chemical stability is achieved. Single and multiple substitutions by atom(s) Z at positions M₁ – M₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. In certain

20

embodiments, R_1 ($-A-M_5-M_{14}$) is to be any substituted atom other than hydrogen or halogen and, may be either a moiety where A may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; furthermore, M_5 , M_6 , M_7 , M_8 , M_9 , M_{10} , M_{11} , M_{12} , M_{13} and M_{14} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by atom(s) Y at positions $M_5 - M_{14}$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R_2 and R_3 are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles. R_4 and R_4' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R_4 and R_4' may be covalently linked to give a set of cyclic compounds.

In another set of embodiments, the composition has a structure:



where M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction and chemical stability is achieved. Single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above

5 designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. In certain embodiments, R_1 ($-A-M_5-M_{14}$) is to be any substituted atom other than hydrogen or halogen and, may be either a moiety where A may be chosen from the set of substituted

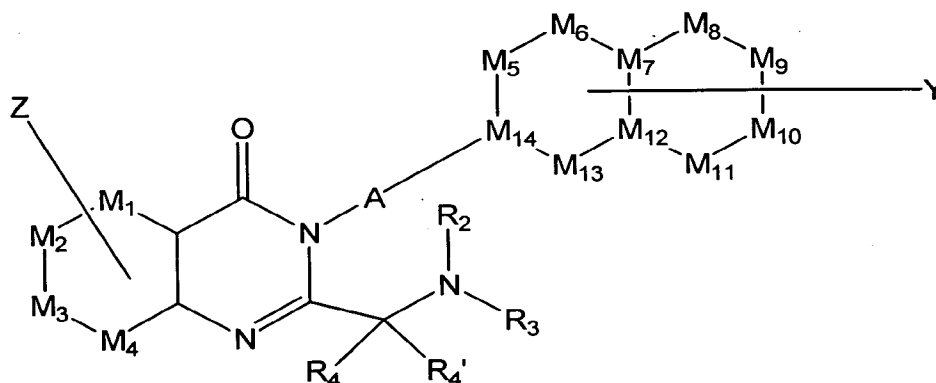
10 carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; furthermore, M_5 , M_6 , M_7 , M_8 , M_9 , M_{10} , M_{11} , M_{12} , M_{13} and M_{14} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved;

15 furthermore, single and multiple substitutions by atom(s) Y at positions $M_5 - M_{14}$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R_2 and R_3 are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with

20 other atoms attached in the latter cases for valance satisfaction; R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles. In certain embodiments, R_2 is a moiety containing at least one atom other than hydrogen and no more than twenty atoms other than hydrogen. R_4 and R_4' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R_4 and

25 R_4' may be covalently linked to give a set of cyclic compounds.

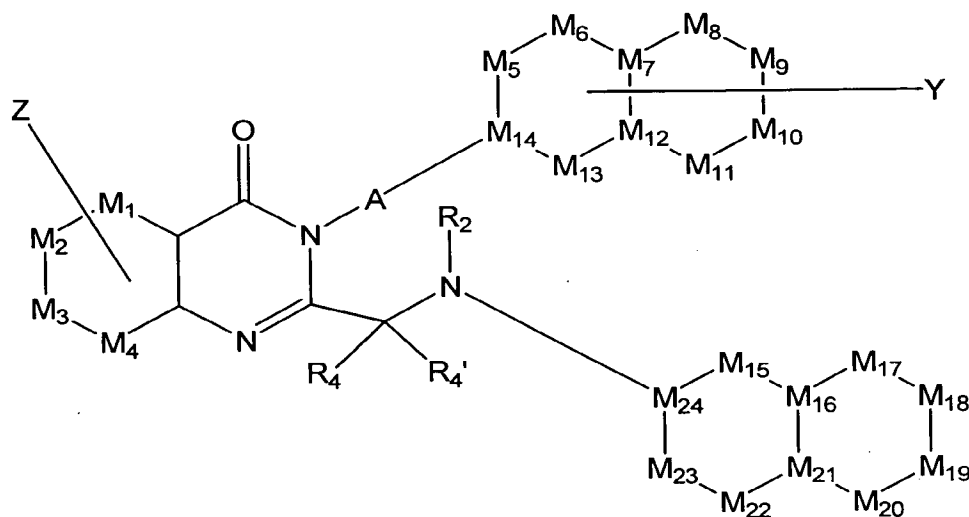
In another set of embodiments, the composition has a structure:



where M₁, M₂, M₃ and M₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused
5 bicyclic ring system providing valance satisfaction and chemical stability is achieved. Single and multiple substitutions by atom(s) Z at positions M₁ – M₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. In certain
10 embodiments, R₁ (-A-M₅-M₁₄) is to be any substituted atom other than hydrogen or halogen and, may be either a moiety where A may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; furthermore, M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are each independently selected from the group consisting of substituted
15 carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or
20 atomic nulls as required for valance satisfaction and chemical stability. R₂ and R₃ are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R₂ and R₃ may be covalently linked to give a set of monocyclic *aza*-cycles. In certain embodiments, R₂ is

a moiety containing two atoms other than hydrogen and no more than eight atoms other than hydrogen. R_4 and R_4' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R_4 and R_4' may be covalently linked to give a set of cyclic compounds.

5 In another set of embodiments, the composition has a structure:



where M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction and chemical stability is achieved. Single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. In certain embodiments, R_1 (-A-M₅-M₁₄) is to be any substituted atom other than hydrogen or halogen and, may be either a moiety where A may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; furthermore, M_5 , M_6 , M_7 , M_8 , M_9 , M_{10} , M_{11} , M_{12} , M_{13} and M_{14} are each independently selected from the group consisting of substituted

carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or

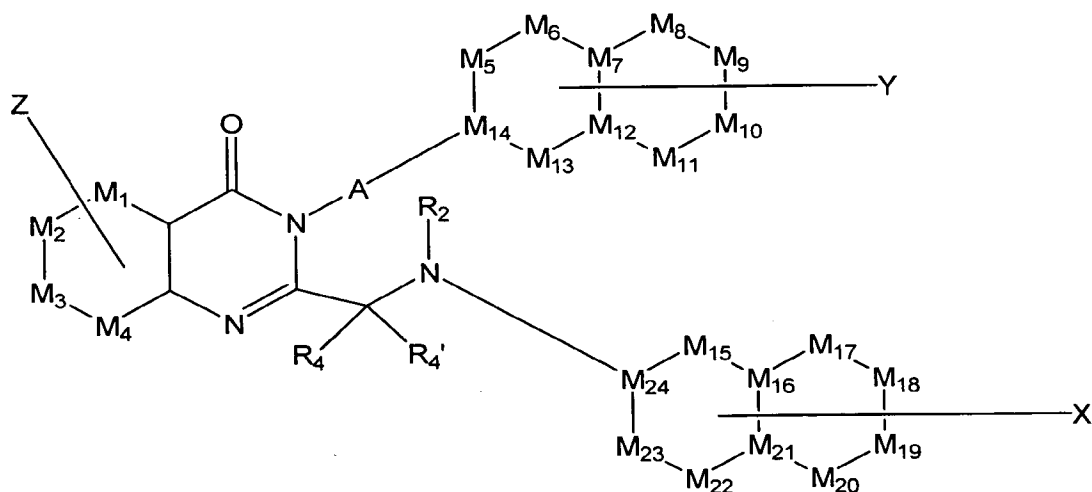
5 substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R₂ and R₃ are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R₂ and R₃ may be covalently linked to give a set of monocyclic *aza*-cycles. In certain embodiments, R₂ is

10 a moiety containing two atoms other than hydrogen and no more than eight atoms other than hydrogen. R₃ (M₁₅-M₂₄) is to be any substituted atom other than hydrogen or halogen and, in certain embodiments, may be either a moiety where M₁₅, M₁₆, M₁₇, M₁₈, M₁₉, M₂₀, M₂₁, M₂₂, M₂₃ and M₂₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such

15 that an acyclic, monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved. R₄ and R_{4'} may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R₄ and R_{4'} may be covalently linked to give a set of cyclic compounds.

In another set of embodiments, the composition has a structure:

20



where M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction and chemical stability is achieved.

5 Single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. In certain embodiments, R_1 ($-A-M_5-M_{14}$) is to be any substituted atom other than hydrogen or

10 halogen and, may be either a moiety where A may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; furthermore, M_5 , M_6 , M_7 , M_8 , M_9 , M_{10} , M_{11} , M_{12} , M_{13} and M_{14} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or

15 bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by atom(s) Y at positions $M_5 - M_{14}$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R_2 and R_3 are

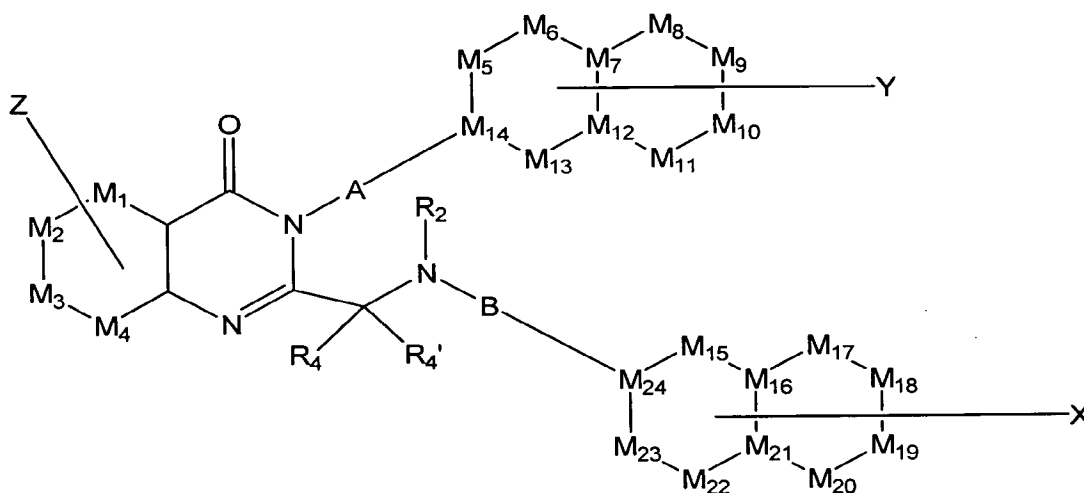
20 each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles. In certain embodiments, R_2 is a moiety containing two atoms other than hydrogen and no more than eight atoms other than hydrogen. R_3 ($M_{15}-M_{24}$) is to be any substituted atom other than hydrogen or

25 halogen and, in certain embodiments, may be either a moiety where M_{15} , M_{16} , M_{17} , M_{18} , M_{19} , M_{20} , M_{21} , M_{22} , M_{23} and M_{24} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that an acyclic, monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by

30 atom(s) X at positions $M_{15} - M_{24}$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur,

boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R_4 and R_4' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R_4 and R_4' may be covalently linked to give a set of cyclic compounds.

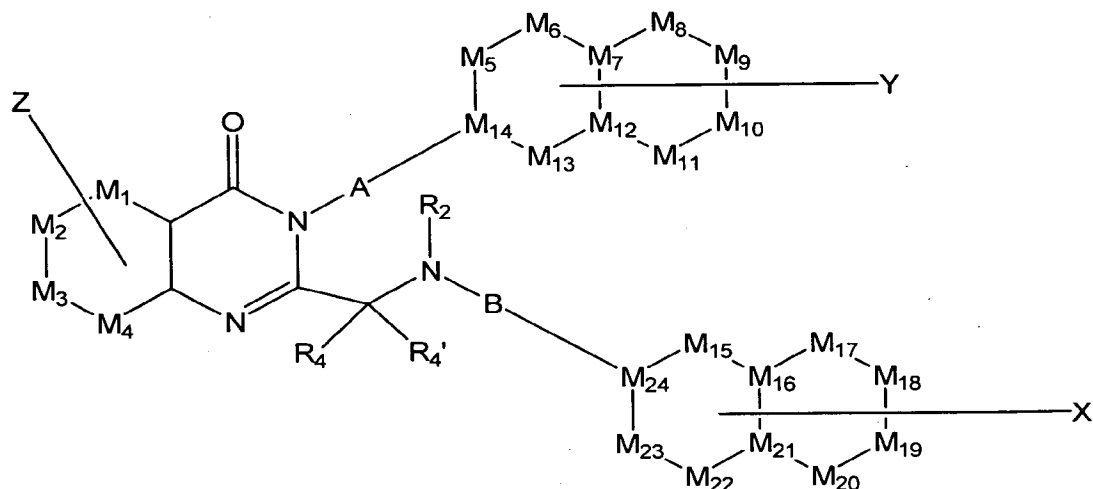
5 In another set of embodiments, the composition has a structure:



where M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused bicyclic ring system providing valance satisfaction and chemical stability is achieved. Single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. In certain embodiments, R_1 ($-A-M_5-M_{14}$) is to be any substituted atom other than hydrogen or halogen and, may be either a moiety where A may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; furthermore, M_5 , M_6 , M_7 , M_8 , M_9 , M_{10} , M_{11} , M_{12} , M_{13} and M_{14} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or

bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by atom(s) Y at positions $M_5 - M_{14}$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R_2 and R_3 are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles. In certain embodiments, R_2 is a moiety containing two atoms other than hydrogen and no more than eight atoms other than hydrogen. In certain embodiments, R_3 (-B- M_{15} - M_{24}) is to be any substituted atom other than hydrogen or halogen and, may be either a moiety where B, a linker, may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; B may be chosen as an atomic null through an octa-atomic set of non-hydrogen atoms such that valance satisfaction and chemical stability are achieved; furthermore, (M_{15} - M_{24}) is to be any substituted atom other than hydrogen or halogen and, in certain embodiments, may be either a moiety where M_{15} , M_{16} , M_{17} , M_{18} , M_{19} , M_{20} , M_{21} , M_{22} , M_{23} and M_{24} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that an acyclic, monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by atom(s) X at positions $M_{15} - M_{24}$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R_4 and R_4' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; R_4 and R_4' may be covalently linked to give a set of cyclic compounds.

In another set of embodiments, the composition has a structure:



where M₁, M₂, M₃ and M₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null such that a fused
 5 bicyclic ring system providing valance satisfaction and chemical stability is achieved. Single and multiple substitutions by atom(s) Z at positions M₁ – M₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. In certain
 10 embodiments, R₁ (-A-M₅-M₁₄) is to be any substituted atom other than hydrogen or halogen and, may be either a moiety where A may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; furthermore, M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are each independently selected from the group consisting of substituted
 15 carbon, nitrogen, sulfur, oxygen and/or an atomic null such that a monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore, single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or
 20 atomic nulls as required for valance satisfaction and chemical stability. R₂ and R₃ are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with

other atoms attached in the latter cases for valance satisfaction; R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles. In certain embodiments, R_2 is a moiety containing two atoms other than hydrogen and no more than eight atoms other than hydrogen. In certain embodiments, R_3 (-B- M_{15} - M_{24}) is to be any substituted atom
5 other than hydrogen or halogen and, may be either a moiety where B, a linker, may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null such that valance satisfaction and chemical stability are achieved; B may be chosen as an atomic null through an octa-atomic set of non-hydrogen atoms such that valance satisfaction and chemical stability are achieved; furthermore, (M_{15} - M_{24}) is to be any
10 substituted atom other than hydrogen or halogen and, in certain embodiments, may be either a moiety where M_{15} , M_{16} , M_{17} , M_{18} , M_{19} , M_{20} , M_{21} , M_{22} , M_{23} and M_{24} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null such that an acyclic, monocyclic or bicyclic ring system providing valance satisfaction and chemical stability are achieved; furthermore,
15 single and multiple substitutions by atom(s) X at positions M_{15} - M_{24} on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls as required for valance satisfaction and chemical stability. R_4 and R_4' may be independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as
20 needed for valance satisfaction; R_4 and R_4' may be covalently linked to give a set of cyclic compounds. In certain embodiments, R_4 and R_4' are chosen to contain from one to twenty atoms such that valance satisfaction and chemical stability are achieved.

In certain embodiments of the invention, whether such embodiments involve a composition, composition including pharmaceutical carrier, or method of making or
25 using a composition, each of such embodiments includes any composition disclosed herein.

Other advantages, novel features, and objects of the invention will become apparent from the following detailed description of non-limiting embodiments of the invention. In cases where the present specification and a document incorporated by
30 reference include conflicting disclosure, the present specification shall control.

Detailed Description of the Invention

Definitions:

The term "MUC1 Growth Factor Receptor" (MGFR) is a functional definition meaning that portion of the MUC1 receptor that interacts with an activating ligand, such as a growth factor or a modifying enzyme such as a cleavage enzyme, to promote cell proliferation. The MGFR region of MUC1 is that extracellular portion that is closest to the cell surface and is defined by most or all of the PSMGFR, as defined below. The MGFR is inclusive of both unmodified peptides and peptides that have undergone enzyme modifications, such as, for example, phosphorylation, glycosylation, etc. Results of the invention are consistent with a mechanism in which this portion is made accessible to the ligand upon MUC1 cleavage at a site associated with tumorigenesis that causes release of the some or all of the IBR from the cell.

The term "Interchain Binding Region" (IBR) is a functional definition meaning that portion of the MUC1 receptor that binds strongly to identical regions of other MUC1 molecules giving MUC1 the ability to aggregate (i.e. self-aggregate) with other MUC1 receptors via the IBRs of the respective receptors. This self-aggregation may contribute to MUC1 receptor clustering, observed in healthy cells.

In a preferred embodiment, the IBR may be approximately defined as a stretch of at least 12 to 18 amino acid sequence within the region of the full-length human MUC1 receptor defined as comprising amino acids 507 to 549 of the extracellular sequence of the MUC1 receptor (SEQ ID NO: 10), with amino acids 525 through 540 and 525 through 549 especially preferred (numbers refer to Andrew Spicer *et al.*, J. Biol. Chem Vol 266 No. 23, 1991 pgs. 15099-15109; these amino acid numbers correspond to numbers 1067, 1109, 1085, 1100, 1085, 1109 of Genbank accession number P15941; PID G547937, SEQ ID NO: 10) or fragments, functional variants or conservative substitutions thereof, as defined in more detail below.

The term "cleaved IBR" means the IBR (or a portion thereof) that has been released from the receptor molecule segment which remains attached to the cell surface. The release may be due to enzymatic or other cleavage of the IBR. As used herein, when the IBR is "at the surface of a cell", it means the IBR is attached to the portion of the cell surface receptor that has not been shed, or cleaved. The cleaved IBR

of interest is a “disease-associated cleavage”, i.e. that type of cleavage that can result in cancer.

The term “Constant Region” (CR) is any non-repeating sequence of MUC1 that exists in a 1:1 ratio with the IBR and forms part of the portion of MUC1 that is shed
5 upon cleavage in healthy and tumorigenic cells.

The term “Repeats” is given its normal meaning in the art.

The term “Primary Sequence of the MUC1 Growth Factor Receptor” (PSMGFR) is a peptide sequence that defines most or all of the MGFR in some cases, and functional variants and fragments of the peptide sequence, as defined below. The
10 PSMGFR is defined as SEQ ID NO: 36 listed below in Table 1, and all functional variants and fragments thereof having any integer value of amino acid substitutions up to 20 (i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) and/or any integer value of amino acid additions or deletions up to 20 at its N-terminus and/or C-terminus. A “functional variant or fragment” in the above context refers to such
15 variant or fragment having the ability to specifically bind to, or otherwise specifically interact with, ligands that specifically bind to, or otherwise specifically interact with, the peptide of SEQ ID NO: 36, while not binding strongly to identical regions of other peptide molecules identical to themselves, such that the peptide molecules would have the ability to aggregate (i.e. self-aggregate) with other identical peptide molecules. One
20 example of a PSMGFR that is a functional variant of the PSMGFR peptide of SEQ NO: 36 (referred to as nat-PSMGFR – for “native”) is SEQ NO: 7 (referred to as var-PSMGFR, which differs from nat-PSMGFR by including an –SPY- sequence instead of the native –SRY- (see bold text in sequence listings)). Var-PSMGFR may have enhanced conformational stability, when compared to the native form, which may be
25 important for certain applications such as for antibody production. The PSMGFR is inclusive of both unmodified peptides and peptides that have undergone enzyme modifications, such as, for example, phosphorylation, glycosylation, etc. A histidine-tagged PSMGFR (e.g. See Table 1 – SEQ ID NO: 2) is abbreviated herein as His-PSMGFR. His-tagged peptide sequences are typically tagged at their C-terminus. In
30 certain embodiments, the invention provides an isolated protein or peptide comprising a PSMGFR, for example at the N-terminus of the protein or peptide, or consisting of a

PSMGFR, wherein the isolated protein or peptide does not comprise any of the amino acid sequences set forth in SEQ IDs: 1, 2, 3, 6, or 7 listed below. In certain embodiments, the invention provides an isolated protein or peptide comprising His-PSMGFR, for example at the N-terminus of the protein or peptide, or consisting of His-PSMGFR, wherein the isolated protein or peptide does not comprise any of the amino acid sequences set forth in SEQ IDs: 1, 2, or 3 listed below.

The term "Extended Sequence of the MUC1 Growth Factor Receptor" (ESMGFR) is a peptide sequence, defined below (See Table 1 – SEQ ID NO: 3), that defines all of His-var-PSMGFR plus 9 amino acids of the proximal end of PSIBR.

The term "Tumor-Specific Extended Sequence of the MUC1 Growth Factor Receptor" (TSESMGFR) is a peptide sequence (See, as an example, Table 1 – SEQ ID NO: 66) that defines a MUC1 cleavage product found in tumor cells that remains attached to the cell surface and is able to interact with activating ligands in a manner similar to the PSMGFR.

PSIBR is a peptide sequence, defined below (See Table 1 – SEQ ID NO: 8), that defines most or all of the IBR.

"Truncated Interchain Binding Region" (TPSIBR) is a peptide sequence defined below (See Table 1 – SEQ ID NO: 65), that defines a smaller portion of the IBR that is released from the cell surface after receptor cleavage in some tumor cells.

PSMGFRTC is a truncated MUC1 receptor isoform comprising PSMGFR and a at or within about up to 30 (i.e. within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) amino acids of its N-terminus and comprising the transmembrane and cytoplasmic sequences of full-length MUC1 receptor. As used herein, The phrase "at its N-terminus" referring to the location of a recited sequence within a larger molecule, such as a polypeptide or receptor, refers to such a sequence being no more than 30 amino acids from the N-terminal amino acid of the molecule. Optionally the PSMGFRTC, as well as the other truncated MUC1 receptor isoforms discussed below, can include a MUC1 N-terminal signaling sequence (Table 1- SEQ ID NO: 47, 58, or 59), typically between 20 and 30 amino acids in length, or a functional fragment or variant thereof. Such a sequence is typically encoded by the nucleic acid constructs encoding the truncated MUC1 receptor isoform

and is translated but is typically cleaved prior to or upon insertion of the receptor in the membrane of the cell. Such a PSMGFRTC, i.e. including the optional signal sequence, would still be a peptide or protein “having a PSMGFR” sequence “at its N-terminus” by the above definition. An example is nat-PSMGFRTC (SEQ ID NO: 37, with or
5 without the signal peptide of SEQ ID NO: 47, 58, or 59 at the extreme N-terminus) having nat-PSMGFR (SEQ NO: 36) at its N-terminus (i.e. at the extreme N-terminal end or within 30 amino acids thereof).

The term “separation” means physical separation from a cell, i.e. a situation in which a portion of MUC 1 that was immobilized with respect to a cell is no longer
10 immobilized with respect to that cell. E.g. in the case of cleavage of a portion of MUC 1, the portion that is cleaved is “separated” if it is free to migrate away from the cell and thereafter may be detected in a bodily fluid, or immobilized at a location remote from the cell from which it was cleaved such as another cell, a lymph node, etc.

The term “binding” refers to the interaction between a corresponding pair of
15 molecules that exhibit mutual affinity or binding capacity, typically specific or non-specific binding or interaction, including biochemical, physiological, and/or pharmaceutical interactions. Biological binding defines a type of interaction that occurs between pairs of molecules including proteins, nucleic acids, glycoproteins, carbohydrates, hormones and the like. Specific examples include antibody/antigen,
20 antibody/hapten, enzyme/substrate, enzyme/inhibitor, enzyme/cofactor, binding protein/substrate, carrier protein/substrate, lectin/carbohydrate, receptor/hormone, receptor/effector, complementary strands of nucleic acid, protein/nucleic acid repressor/inducer, ligand/cell surface receptor, virus/ligand, etc.

The term “binding partner” refers to a molecule that can undergo binding with a
25 particular molecule. Biological binding partners are examples. For example, Protein A is a binding partner of the biological molecule IgG, and vice versa.

The term “aggregate” (noun) means a plurality of cell surface receptors or fragments thereof (e.g. MUC 1) immobilized with respect to each other with or without an intermediate auxiliary to the host system. This includes self-aggregation of healthy
30 receptors at a cell surface; self-aggregation of cleaved receptors or fragments bound to each other; cleaved receptors or fragments bound to receptors or fragments attached to

a cell surface; receptors or fragments, whether attached to a cell or cleaved, immobilized with respect to each other via an intermediate auxiliary to the host. "Intermediate auxiliary to the host system" includes a synthetic species such as a polymer, dendrimer, etc., or a naturally-occurring species, for example an IgM antibody, which is not simply naturally present in the host system but is added to the host system from a source external to the host system. This excludes aggregation that is the result of an intermediate naturally present in the host system such as a growth factor that can cause disease-associated aggregation ("Inductive multimerization"). "Aggregate" (verb) or "aggregation" means the process of forming an aggregate (noun).

"Inductive multimerization" refers to aggregation wherein the aggregate formed can act to induce the cells to grow or proliferate. Inductive multimerization typically involves dimerization or tetramerization of cell surface receptors, for example by a growth factor or other activating ligand, but can also involve higher order multimerization, so long as the degree of multimerization is not so great as to mimic natural receptor clustering, in a particular cell type, which prevents receptors from signaling the cell to grow or proliferate.

"Preventative clustering" refers to multimerization of receptors to form an aggregate involving a sufficient number of receptors to mimic natural receptor clustering, in a particular cell type, which prevents receptors from signaling the cell to grow or proliferate, for example with an intermediate auxiliary to the host system.

A "ligand" to a cell surface receptor, refers to any substance that can interact with the receptor to temporarily or permanently alter its structure and/or function. Examples include, but are not limited to binding partners of the receptor, (e.g. antibodies or antigen-binding fragments thereof), and agents able to alter the chemical structure of the receptor (e.g. modifying enzymes).

An "activating ligand" refers to a ligand able interact with a receptor to transduce a signal to the cell. Activating ligands can include, but are not limited to, species that effect inductive multimerization of cell surface receptors such as a single molecular species with greater than one active site able to bind to a receptor; a dimer, a tetramer, a higher multimer, a bivalent antibody or bivalent antigen-binding fragment

thereof, or a complex comprising a plurality of molecular species. Activating ligands can also include species that modify the receptor such that the receptor then transmits a signal. Enzymes can also be activating ligands when they modify a receptor to make it a new recognition site for other activating ligands, e.g. glycosylases are activating
5 ligands when the addition of carbohydrates enhances the affinity of a ligand for the receptor. Cleavage enzymes are activating ligands when the cleavage product is the more active form of the receptor, e.g. by making a recognition site for a ligand more accessible. In the context of MUC1 tumor cells, an activating ligand can be a species that cleaves MUC1, chemically modifies the receptor, or species that interact with the
10 MGFRs on the surface of the MUC1 tumor cells to transduce a signal to the cell that stimulates proliferation, e.g. a species that effects inductive multimerization.

A "growth factor" refers to a species that may or may not fall into a class of previously-identified growth factors, but which acts as a growth factor in that it acts as an activating ligand.

15 A "MUC1 presenting cell" refers to both non-cancerous and cancerous cells expressing MUC1 and/or MGFRs on the surface. A "MUC1 tumor cell" or "MUC1 cancer cell" or "cancerous MUC1 cell" refers to a cancerous tumor cell that aberrantly expresses MUC1 and/or MGFR on its surface.

"Colloids", as used herein, means nanoparticles, i.e. very small, self-
20 suspendable or fluid-suspendable particles including those made of material that is, e.g., inorganic or organic, polymeric, ceramic, semiconductor, metallic (e.g. gold), non-metallic, crystalline, amorphous, or a combination. Typically, colloid particles used in accordance with the invention are of less than 250 nm cross section in any dimension, more typically less than 100 nm cross section in any dimension, and in most cases are
25 of about 2-30 nm cross section. One class of colloids suitable for use in the invention is 10-30 nm in cross section, and another about 2-10 nm in cross section. As used herein this term includes the definition commonly used in the field of biochemistry.

As used herein, a component that is "immobilized relative to" another component either is fastened to the other component or is indirectly fastened to the
30 other component, e.g., by being fastened to a third component to which the other component also is fastened, or otherwise is transitionally associated with the other

component. For example, a signaling entity is immobilized with respect to a binding species if the signaling entity is fastened to the binding species, is fastened to a colloid particle to which the binding species is fastened, is fastened to a dendrimer or polymer to which the binding species is fastened, etc. A colloid particle is immobilized relative
5 to another colloid particle if a species fastened to the surface of the first colloid particle attaches to an entity, and a species on the surface of the second colloid particle attaches to the same entity, where the entity can be a single entity, a complex entity of multiple species, a cell, another particle, etc.

“Signaling entity” means an entity that is capable of indicating its existence in a
10 particular sample or at a particular location. Signaling entities of the invention can be those that are identifiable by the unaided human eye, those that may be invisible in isolation but may be detectable by the unaided human eye if in sufficient quantity (e.g., colloid particles), entities that absorb or emit electromagnetic radiation at a level or within a wavelength range such that they can be readily detected visibly (unaided or
15 with a microscope including an electron microscope or the like), or spectroscopically, entities that can be detected electronically or electrochemically, such as redox-active molecules exhibiting a characteristic oxidation/reduction pattern upon exposure to appropriate activation energy (“electronic signaling entities”), or the like. Examples include dyes, pigments, electroactive molecules such as redox-active molecules,
20 fluorescent moieties (including, by definition, phosphorescent moieties), up-regulating phosphors, chemiluminescent entities, electrochemiluminescent entities, or enzyme-linked signaling moieties including horseradish peroxidase and alkaline phosphatase. “Precursors of signaling entities” are entities that by themselves may not have signaling capability but, upon chemical, electrochemical, electrical, magnetic, or physical
25 interaction with another species, become signaling entities. An example includes a chromophore having the ability to emit radiation within a particular, detectable wavelength only upon chemical interaction with another molecule. Precursors of signaling entities are distinguishable from, but are included within the definition of, “signaling entities” as used herein.

30 As used herein, “fastened to or adapted to be fastened”, in the context of a species relative to another species or to a surface of an article, means that the species is

chemically or biochemically linked via covalent attachment, attachment via specific biological binding (e.g., biotin/streptavidin), coordinative bonding such as chelate/metal binding, or the like. For example, "fastened" in this context includes multiple chemical linkages, multiple chemical/biological linkages, etc., including, but
5 not limited to, a binding species such as a peptide synthesized on a polystyrene bead, a binding species specifically biologically coupled to an antibody which is bound to a protein such as protein A, which is attached to a bead, a binding species that forms a part (via genetic engineering) of a molecule such as GST or Phage, which in turn is specifically biologically bound to a binding partner covalently fastened to a surface
10 (e.g., glutathione in the case of GST), etc. As another example, a moiety covalently linked to a thiol is adapted to be fastened to a gold surface since thiols bind gold covalently. Similarly, a species carrying a metal binding tag is adapted to be fastened to a surface that carries a molecule covalently attached to the surface (such as thiol/gold binding) which molecule also presents a chelate coordinating a metal. A species also is
15 adapted to be fastened to a surface if a surface carries a particular nucleotide sequence, and the species includes a complementary nucleotide sequence.

"Covalently fastened" means fastened via nothing other than one or more covalent bonds. E.g. a species that is covalently coupled, via EDC/NHS chemistry, to a carboxylate-presenting alkyl thiol which is in turn fastened to a gold surface, is
20 covalently fastened to that surface.

"Specifically fastened" or "adapted to be specifically fastened" means a species is chemically or biochemically linked to another specimen or to a surface as described above with respect to the definition of "fastened to or adapted to be fastened", but excluding all non-specific binding.

25 Certain embodiments of the invention make use of self-assembled monolayers (SAMs) on surfaces, such as surfaces of colloid particles, and articles such as colloid particles having surfaces coated with SAMs. In one set of embodiments, SAMs formed completely of synthetic molecules completely cover a surface or a region of a surface, e.g. completely cover the surface of a colloid particle. "Synthetic molecule", in this
30 context, means a molecule that is not naturally occurring, rather, one synthesized under the direction of human or human-created or human-directed control. "Completely

cover” in this context, means that there is no portion of the surface or region that directly contacts a protein, antibody, or other species that prevents complete, direct coverage with the SAM. I.e. in certain embodiments the surface or region includes, across its entirety, a SAM consisting completely of non-naturally-occurring molecules (i.e. synthetic molecules). The SAM can be made up completely of SAM-forming species that form close-packed SAMs at surfaces, or these species in combination with molecular wires or other species able to promote electronic communication through the SAM (including defect-promoting species able to participate in a SAM), or other species able to participate in a SAM, and any combination of these. Preferably, all of the species that participate in the SAM include a functionality that binds, optionally covalently, to the surface, such as a thiol which will bind to a gold surface covalently. A self-assembled monolayer on a surface, in accordance with certain embodiments of the invention, can be comprised of a mixture of species (e.g. thiol species when gold is the surface) that can present (expose) essentially any chemical or biological functionality. For example, they can include tri-ethylene glycol-terminated species (e.g. tri-ethylene glycol-terminated thiols) to resist non-specific adsorption, and other species (e.g. thiols) terminating in a binding partner of an affinity tag, e.g. terminating in a chelate that can coordinate a metal such as nitrilotriacetic acid which, when in complex with nickel atoms, captures a metal binding tagged-species such as a histidine-tagged binding species. Also disclosed is a method for rigorously controlling the concentration of essentially any chemical or biological species presented on a colloid surface or any other surface. Without this rigorous control over peptide density on each colloid particle, co-immobilized peptides would readily aggregate with each other to form micro-hydrophobic-domains that would catalyze colloid-colloid aggregation in the absence of aggregate-forming species present in a sample. This is an advantage of certain embodiments of the present invention, over existing colloid agglutination assays. In many embodiments of the invention the self-assembled monolayer is formed on gold colloid particles.

The kits described herein, contain one or more containers, which can contain compounds such as the species, signaling entities, biomolecules, and/or particles as described. The kits also may contain instructions for mixing, diluting, and/or

administering the compounds. The kits also can include other containers with one or more solvents, surfactants, preservative and/or diluents (e.g. normal saline (0.9% NaCl, or 5% dextrose) as well as containers for mixing, diluting or administering the components to the sample or to the patient in need of such treatment.

5 The compounds in the kit may be provided as liquid solutions or as dried powders. When the compound provided is a dry powder, the powder may be reconstituted by the addition of a suitable solvent, which also may be provided. Liquid forms of the compounds may be concentrated or ready to use. The solvent will depend on the compound and the mode of use or administration. Suitable solvents for are well
10 known for drug compounds and are available in the literature.

 The term "cancer", as used herein, may include but is not limited to: biliary tract cancer; bladder cancer; brain cancer including glioblastomas and medulloblastomas; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms including acute
15 lymphocytic and myelogenous leukemia; multiple myeloma; AIDS-associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer including squamous cell carcinoma; ovarian cancer including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreatic cancer; prostate cancer;
20 rectal cancer; sarcomas including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Kaposi's sarcoma, basocellular cancer, and squamous cell cancer; testicular cancer including germinal tumors such as seminoma, non-seminoma (teratomas, choriocarcinomas), stromal
25 tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor. Preferred cancers are; breast, prostate, lung, ovarian, colorectal, and brain cancer.

 The term "cancer treatment" as described herein, may include but is not limited to: chemotherapy, radiotherapy, adjuvant therapy, or any combination of the
30 aforementioned methods. Aspects of treatment that may vary include, but are not limited to: dosages, timing of administration, or duration or therapy; and may or may

not be combined with other treatments, which may also vary in dosage, timing, or duration. Another treatment for cancer is surgery, which can be utilized either alone or in combination with any of the aforementioned treatment methods. One of ordinary skill in the medical arts may determine an appropriate treatment.

5 An “agent for prevention of cancer or tumorigenesis” means any agent that counteracts any process associated with cancer or tumorigenesis described herein. For example, an agent that interacts with (e.g. binds to) to MGFR thereby reducing or preventing interaction, with MGFR, of an agent that promotes tumorigenesis by its interaction with MGFR.

10 An “agent that reduces cleavage of a cell surface receptor interchain binding region” as used herein is any composition that prevents or reduces cleavage of the MUC1 receptor between the MGFR and the N-terminus of the IBR that would otherwise occur in the absence of the agent. Cleavage of the receptor between the MGFR and the N-terminus of the IBR can be caused by activity of enzymes that are
15 membrane-associated or soluble, e.g. matrix metalloproteases (MMPs and MT-MMPs). Some of these enzymes are directly responsible for cleavage. Other enzymes can affect cleavage, (e.g. prevent cleavage at a particular location) by modifying MUC1 with sugar groups or phosphates that mask a recognition epitope associated with cleavage. Other enzymes can promote cleavage at a particular location by modifying MUC1 with
20 sugar groups or phosphates that create a recognition motif for cleavage at that location. Other enzymes can promote cleavage of receptors by activating other cleavage enzymes. One way to select agents that reduce cleavage of a cell surface receptor IBR is to first identify enzymes that affect cleavage as described above, and screen agents, and their analogs, for their ability to alter the activity of those enzymes. Another way is
25 to test agents that are known to affect the activity of similar enzymes (e.g. from the same family) for their ability to alter the site of cleavage of MUC1, and to similarly test analogs of these agents. Alternatively, agents are screened in a cell-free assay containing the enzyme and MUC1 receptors, and the rate or position of cleavage measured by antibody probing, Polymerase Chain Reaction (PCR), or the like.
30 Alternatively, without first identifying enzymes that affect MUC1, agents are screened against cells that present MUC1 for the agents’ ability to alter cleavage site or the rate

of cleavage of MUC1. For example, agents can be screened in an assay containing whole cells that present MUC1 and aggregation potential of the cell supernatant can be measured, an indication of the amount of IBR that remains attached to the cleaved portion of MUC1, i.e. the degree of cleavage between MGFR and IBR. In another
5 technique, agents can be screened in an assay containing whole cells that present MUC1, the supernatant removed, and the cell remain tested for accessibility of the MGFR portion, e.g. using a labeled antibody to the MGFR. Agents can be identified from commercially available sources such as molecular libraries, or rationally designed based on known agents having the same functional capacity and tested for activity
10 using the screening assays.

An "agent that reduces cleavage of the MUC1 receptor" is any composition that prevents or reduces cleavage of the MUC1 receptor at any location. Such an agent can be used to treat a subject having cancer or at risk for developing cancer because if cleavage is prevented, then the accessibility of the MGFR, a functional receptor
15 associated with cancer, is reduced or prevented. Such agents can be selected by exposing cells to a candidate agent and determine, in the supernatant, the amount of cleaved MUC1 receptor, relative to a control.

A subject, as used herein, refers to any mammal (preferably, a human), and preferably a mammal that may be susceptible to tumorigenesis or cancer associated
20 with the aberrant expression of MUC1. Examples include a human, non-human primate, cow, horse, pig, sheep, goat, dog, or cat. Generally, the invention is directed toward use with humans.

The samples used herein are any body tissue or body fluid sample obtained from a subject. Preferred are body fluids, for example lymph, saliva, blood, urine, milk
25 and breast secretions, and the like. Blood is preferred in certain embodiments. Samples of tissue and/or cells for use in the various methods described herein can be obtained through standard methods including, but not limited to: tissue biopsy, including punch biopsy and cell scraping, needle biopsy, and collection of blood or other bodily fluids by aspiration or other methods.

30 The present invention, in certain embodiments, involves compositions and methods for cancer treatment and, in particular, to compositions that are able to inhibit

interactions involving the MUC1 Growth Factor Receptor and/or its ligands, and methods for treating patients displaying symptoms of, or susceptible to MUC1-associated cancers. The invention also relates to assays and/or use of such compositions for the treatment of patients susceptible to or exhibiting symptoms
5 characteristic of cancer or tumorigenesis. Other compositions of certain embodiments of the present invention useful for the treatment or prevention of cancer or tumorigenesis include homologs, analogs, derivatives, enantiomers or functional equivalents of compositions disclosed herein. Assays can be performed, according to certain embodiments of the invention, to screen for and identify such compositions, and
10 also for identifying which compositions are effective at various stages of the disease process.

The present invention, in certain embodiments, involves compositions and methods for the treatment or prevention of proliferative disorders, including cancers, and in particular to those proliferative disorders that involve the cell surface receptor
15 MUC1. In another aspect, the invention relates to the discovery of a variety of compositions (e.g., drugs) useful for inhibition of cell proliferation, including proliferation associated with tumors such as MUC1-related tumors. The invention, in certain embodiments, also relates to diagnostic methods for determining whether the proliferative disorder involves MUC1 and then linking these diagnostic methods to
20 determining effective treatments for those conditions that involve MUC1. The invention also relates to diagnostic methods that can then be used to track the progress of patient in response to these treatments. In yet another aspect, the invention relates to the discovery of a variety of compositions (e.g., drugs) useful for inhibition of cell proliferation, including proliferation associated with tumors that involves compositions
25 that can abstract a metal, and in particular can abstract a Mg or Zn cation from metal dependent proteins, such as kinesins and matrix metalloproteases. The compositions of the present invention can be provided in a kit including instructions for use of the composition for treatment of diseases.

MUC1 is a cell surface receptor that is aberrantly expressed in a number of
30 cancers. It has been observed that in a healthy cell the receptor is clustered at the apical border and on a tumor cell, the receptors are distributed over the entire cell surface. It

is known that the MUC1 receptor can be cleaved and it is also known that the receptor under some circumstances can shuttle between states of cell surface expression and cellular internalization.

The present invention involves, in certain embodiments, compounds for the treatment or prevention of proliferative diseases including cancers. Particularly described are compounds for the treatment of cancers wherein the cells of the cancer present the cell surface receptor MUC1. Many of these compounds inhibit, either directly or indirectly, the MUC1 receptor and by so doing inhibit the growth of MUC1-positive tumor cells. These compounds can be administered to a patient for the treatment or prevention of MUC1-positive cancers. Compounds that inhibit MUC1 cancers can act by a variety of mechanisms described herein. In certain embodiments, the compounds bind to the MGFR portion of the receptor and inhibit its growth factor activity. Other compounds described herein inhibit the MUC1 receptor indirectly by inhibiting enzymes that cleave the receptor. In certain embodiments, compounds are described that bind to the MUC1 receptor and also have a metal chelate functionality, which inactivates metal-dependent proteins and thus inhibits MUC1 cleavage. Methods are also described for disabling the tumorigenic activity of the MUC1 receptor via the use of agents that inhibit the expression of MUC1, e.g. through the use of anti-sense DNA or inhibitory RNAs called RNAi, inhibit the proteolysis of MUC1, inhibit post-translational modifications of MUC1 and inhibit natural ligands of MUC1 either directly or indirectly. Other compounds described herein act on intracellular proteins and are delivered to the intracellular region by MUC1 as it shuttles from the cell surface to the interior of the cell. Compounds are described that inhibit cell proliferation by inhibiting proteins from the kinesin family and in particular embodiments inhibit these proteins by abstracting a cationic metal from them. Compounds having the ability to chelate a cationic metal are also described, wherein they inhibit the activity of enzymes and receptors by removing or scavenging physiologically relevant cationic metals.

It has been reported that the MUC1 receptor can be cleaved, releasing a portion of the receptor and leaving a portion attached to the cell surface. Elevated levels of the shed portion of MUC1 can be detected in the blood of Stage II and III breast cancer

patients. These levels increase as cancer progresses, which implies that receptor cleavage and cancer progression are related. The inventors have reported in a previous application (see, e.g. U.S. Patent Application Publication Nos. 2003/0036199 A1 and 2003/0130293 A1) that cleavage products that remain attached to the cell surface are
5 preferentially produced in tumor cells. These low molecular weight species are the result of cleavage, which occurs at at least two different sites and run with an apparent molecular weight of approximately 20kD after deglycosylation. The portions that remain attached to the cell surface may consist essentially of PSMGFR (SEQ ID NO: 36) or TSESMGFR (SEQ ID NO: 66). The inventors previously disclosed that the
10 PSMGFR (Table 1, SEQ. ID No. 36) portion of the MUC1 receptor can be the necessary and sufficient extracellular portion of the receptor that mediates cell growth and enables anchorage-independent cell growth, which is a characteristic of tumor cells. Therefore, agents that bind to the PSMGFR or to the ESPSMGFR may be therapeutics for the treatment or prevention of MUC1-positive cancers. Since the
15 MUC1 cleavage product is linked to the growth factor activity of MUC1 and tumorigenesis, even more potent therapeutics may be compounds that can bind to the MUC1 receptor and block its interactions with activating ligands and also possess a functionality that prevents cleavage of the receptor. Also effective may be compounds that can bind the MUC1 receptor and have a metal chelate functionality to inhibit
20 MUC1 cleavage by a metalloprotease. In certain embodiments, preferred are compounds from the quinazolinone family and from the mp- benzthiophene equivalent family that also possess a metal chelate function.

Until now, the enzyme(s) that cleaves MUC1 was unknown. Because the amount of shed MUC1 receptor found in the blood increases with the progression of the
25 disease and because the inventors previously disclosed that the cleavage product PSMGFR could be the necessary and sufficient portion of the receptor that mediates the growth factor activity of the receptor, the present inventors have determined, in the context of certain aspects of the invention, that agents that inhibit the enzymes that are able to cleave MUC1 are therapeutic targets for the treatment and prevention of
30 MUC1-positive cancers. It has been reported that some of the MMPs (matrix metalloproteases) are over-expressed in cancers and certain phosphatase inhibitors that

induce expression of some MMPs have been shown to both increase cell proliferation and increase the shedding of MUC1. However there are numerous MMPs and ADAMs, which cleave a variety of substrates some of which may be related to cancer and some not. Therefore, in the context of the design and/or discovery of therapeutics, one aspect
5 of the invention involves methods to determine which metalloproteases cleave what substrates and to determine the biological outcome of the inhibition of each.

Agents that inhibit MUC1 cleavage may be used to treat patients with MUC1-positive cancers. The present inventors have determined in the context of certain aspects of the present invention, that agents that inhibit Furin inhibits the cleavage of
10 MUC1, and thus can be used to treat or prevent MUC1-positive cancers. Furin is an enzyme that cleaves a pro-domain from other enzymes and this cleavage is required for them to be in their active state. Furin processes the six MT-MMPs from the pro-enzyme to their active state. TIMPs (tissue inhibitors of metalloproteases) are small proteins that bind to and inhibit the cleavage activity of several MMPs. The present
15 inventors have determined in the context of certain aspects of the present invention, that TIMP 2 and TIMP 3 inhibited the cleavage of MUC1. MT1-MMP, which is also known as MMP-14, is processed to its active state by Furin. Further, TIMP 2 and TIMP 3 are known to inhibit MT1-MMP. It is herein disclosed that MT1-MMP is able to cleave MUC1 to produce cleavage products that function as growth factor receptors
20 and may consist essentially of the PSMGFR and/or the ESPSMGFR. Thus, inhibitors of MT1-MMP may be therapeutics for the treatment of MUC1-positive cancers. The present specification also discloses, in the context of certain aspects of the invention, that TIMPS 2 and 3 inhibit the cleavage of MUC1 and thus may be therapeutics for the treatment of MUC1-positive cancers. Since these cleavage enzymes are dependent on
25 the presence of Zn for activity, agents that chelate Zn are preferred, in certain embodiments, as therapeutic agents for the inhibition of MUC1-positive cancers. In certain embodiments, therapeutic agents for the treatment of MUC1 cancers are agents that can bind to the MGFR region of the MUC1 receptor and also have a metal chelate functionality wherein the agent can chelate Zn or Mg.

30 The compound shown in Tables 4, Compound No.173, has a metal chelate moiety that is able to chelate Mg, Zn and Ni. The compound shown in Table 2,

Compound No. 96, has a metal chelate functionality and is able to chelate the metals Mg and Zn. Therefore, these two compounds are able to inhibit metal-dependent proteins and particularly metal-dependent cleavage enzymes. It has also been discovered in the context of certain embodiments of the present invention, that

5 Compounds Nos. 173 and 96 inhibit cleavage of MUC1. These compounds also have the ability to bind to the MGFR portion of MUC1 and thus can be especially potent inhibitors of cell proliferation because they bind to and block the growth factor receptor portion of MUC1 and also localize the metal chelate functionality to a position near the site where a metal-dependent protease would cleave MUC1. Compounds Nos.173 and

10 96 are dual function compounds that can inhibit cleavage of MUC1 to prevent the production of the growth factor receptor form of the receptor and also block the interaction of the MGFR with its activating ligands. Thus, Compounds Nos.173 and 96 may be excellent therapeutics for the treatment of MUC1-positive cancers and other proliferative disorders that involve the MUC1 receptor. More broadly, Compounds

15 Nos.173 and 96 may be therapeutics for conditions in which the inhibition of a metal-dependent protein has beneficial effects. Compounds Nos.173 and 96 and similar compounds, e.g. those having a metal chelate functionality and in certain embodiments a metal chelate functionality and a motif that increases the concentration of the compound at the target site, can potentially be used to treat essentially any condition

20 mediated by metal-dependent proteins. For example, these types of compounds can be, or can potentially be, used to treat proliferative diseases, including cancers that are mediated by Hedgehog proteins and particularly Sonic Hedgehog proteins by abstracting a metal from the hedgehog protein itself or by abstracting a Zn metal from Cos 2 (Costal2), which is a kinesin-like protein that is operative in the intracellular

25 hedgehog signaling pathway. Compounds Nos.173 and 96 and similar agents that can chelate Mg can also be therapeutic agents for the treatment of cancers because they abstract a Mg atom from KSP (kinesin spindle protein) and inhibit its processing of ATP. Compounds with a metal chelate function can also be used to treat diseases that are mediated by proteins that span the membrane multiple times and involve a metal,

30 the removal of which causes that loop to be internalized by the cell to shut down signaling. An example of this type of receptor is the melatonin hormone receptor

which complexes Zn on one of the loops. Removal of the Zn atom causes that loop to be internalized and affects the regulation of the signal.

It is known that some cell surface receptors shuttle back and forth from the cell surface to the interior of the cell. It has been previously reported that MUC1 receptor
5 shuttles from the cell surface to the cell interior. It has been proposed that the MUC1 receptor is glycosylated during this shuttling process. The present invention, in certain embodiments, provides a method whereby the shuttling mechanism of the MUC1 receptor is exploited to deliver compounds to the cell interior where they act on intracellular targets. For example, Compounds Nos. 173 and 96 have a functionality
10 that allows them to bind to the MGFR portion of the MUC1 receptor and a functionality that chelates a metal. According to an embodiment of the inventive method, the shuttling mechanism of the MUC1 receptor can be exploited to cause the concentration of Compounds Nos. 173 and 96 within MUC1-positive cells to be much higher than in other cells, thereby concentrating the agent at the site of therapeutic
15 interest. Within the cell, these compounds may abstract Mg or Zn from proteins that are required for cell division, e.g. KSP and Costal2 (Cos2). Therapeutic compounds that have a first functionality that binds to a cell surface receptor that shuttles back and forth across the cell membrane and a second functionality that acts on intracellular targets may be especially effective therapeutics. Preferred compounds, for certain
20 embodiments, are those that have a first functionality that binds to a portion of a receptor that can be internalized and a second functionality that chelates a metal. Preferred, in certain embodiments, are compounds that have a first functionality that binds to the PSMGFR (SEQ. No 36) and/or the TSESMGFR (SEQ. No 66) and a second functionality that chelates Mg, Zn and/or Ca. In certain embodiments, the
25 portion that binds to the PSMGFR and/or TSESMGFR is from the quinazolinone family and the metal chelate functionality can chelate magnesium and/or zinc, to inactivate KSP and/or Cos 2.

It is beneficial to determine whether or not cancers present the MUC1 receptor because its aberrant expression has been observed in a large percentage of cancers.
30 Anti-proliferative compounds that act on the MUC1 receptor and/or on the MUC1 signaling pathway are described herein and have been previously reported.

Therapeutics that act through a MUC1 mechanism would typically not be effective in MUC1-negative cancers, and therapeutic agents that act on MUC1 and/or a MUC1-related pathway could be especially effective against cancers that present the MUC1 receptor. Therefore, to provide more effective patient care it is, as taught in the context of certain embodiments of the invention, desirable that cancers be characterized to determine whether or not they present the MUC1 receptor. Specimens can be analyzed, according to certain embodiments of the invention, for the presence of MUC1 to determine an appropriate course of treatment, for example administration of one or more compositions of the invention, and/or to determine a patient population susceptible to benefit from treatment with a composition disclosed herein (e.g. a population having a cancer characterized by aberrant expression of MUC1). A further indication of the involvement of the MUC1 receptor in the progression of cancers wherein the MUC1 receptor is present is the determination of a loss of MUC1 receptor clustering. The presence of the MUC1 receptor in patient specimens will guide the physician in the selection of treatments.

A variety of standard and non-standard methods can be employed to determine whether a specimen contains the MUC1 receptor. In the most simple case, a biopsy specimen is stained with an antibody, such as CA15.3 (Roche Diagnostic) or CA 27.29 (Biomira), which recognize the tandem repeat units of the MUC1 receptor. The probe antibody is either optically active or is reacted with a secondary antibody that is optically active. Thus, visual inspection of the stained specimen reveals whether or not the tumor was MUC1 positive or negative and suitable therapies can be determined.

Those skilled in the art will appreciate that there are several techniques suitable for determining the presence of the MUC1 receptor in a sample. One such method involves analyzing nucleic acids, which may include DNA or RNA, to determine if they contain MUC1 sequences. Antibodies and other ligands that specifically recognize portions of the MUC1 receptor are also used to probe for the presence of the receptor in, for example, sandwich assays such as ELISAs and western blots assays to determine the presence of the MUC1 receptor or portions thereof in the specimen. Chemiluminescent technology can also be used to determine binding of a recognition agent to the MUC1 receptor. An example of an antibody that has been used to probe

for the presence of the MUC1 receptor in samples is CA 15.3. This antibody and others recognize portions of the MUC1 receptor that are distal to the cell surface and which contain tandem repeat units. These and other cognate entities can be used in any assay that indicates the presence of the MUC1 receptor or portions thereof.

5 However, because the MUC1 receptor is subject to proteolysis, use of diagnostic antibodies recognizing certain portions of the receptor may be advantageous over use of those recognizing others. The present specification teaches that proteolyzed MUC1 is preferentially produced in tumor cells, the extracellular portion of the cleavage products of which may consist essentially of PSMGFR and TSESMGFR.

10 Additionally, the inventors have discovered that the PSMGFR can be the necessary and sufficient portion of the MUC1 receptor that mediates cell growth and enables anchorage-independent cell growth, which is characteristic of tumor cells.

 Antibodies against the tandem repeat units of the MUC1 receptor are commercially available and can be used as diagnostic reagents. However, these
15 antibodies are of limited use to detect MUC1 in samples derived from cells or tissue specimens, especially when the samples are derived from a tumor, for a number of reasons. On tumor cells, many of the receptors are typically cleaved, so that the tandem repeat units are no longer attached to the cell surface. This means that probing a patient specimen with this antibody will produce conflicting results. In an extreme case,
20 wherein all of the MUC1 receptors have been cleaved to the MGFR form, which functions as a growth factor receptor, the diagnostic assay would read MUC1-negative reflecting the lack of tandem repeats but missing the fact that the growth factor form was fully expressed. If a patient's specimen has a low level of reactivity with the antibody against the terminal repeats, it may be because there is a low level of MUC1
25 expressed on the cell surface or there is a high level of receptor cleavage and by extension a high level of tumor cell proliferation. A further complication of using antibodies that bind to the tandem repeat units is that the number of repeats varies from person to person and this variation has not been linked to cancer. Therefore, a high level of antibody reactivity with a patient specimen may mean that there is a lot of
30 MUC1 receptor expressed on the surface of the cells or may mean that the patient

expresses MUC1 with a greater than average number of repeat units attached to each receptor.

Antibodies against the cytoplasmic tail of MUC1 are available. These antibodies could be used to probe patient specimens that have been processed such that they are amenable to analysis using SDS-PAGE or western blots. Using this type of assay, the antibody against the cytoplasmic tail could reveal whether or not the MUC1 receptor was expressed in the specimen and the approximate molecular weights of the expressed MUC1 species, but would not provide any information about receptor clustering or patterning on the cell surface. Additionally, these assays are lengthy and labor intensive.

Antibodies that recognize portions of the UR may be useful for some diagnostic purposes, but since this portion of the MUC1 receptor is typically shed from the cell surface following MUC1 cleavage in tumor cells, its use as a diagnostic reagent for probing tissues and cells would be limited. An antibody that recognizes this portion of the receptor may be useful for determining the ratio of cleaved to uncleaved receptor.

Antibodies that bind to the MGFR portion of the MUC1 receptor are preferred, in certain embodiments, as diagnostic reagent for probing cells and tissue specimens. In certain embodiments, the MUC1 diagnostic antibody recognizes a portion or portions of the ESPSMGFR. In certain embodiments, the MUC1 diagnostic antibody recognizes a portion or portions of the PSMGFR. The inventors have determined that an antibody raised to the PSMGFR (SEQ ID NO: 36) specifically binds to the MUC1 receptor, whether it is the full-length receptor or the proteolyzed fragment, which is produced by tumor cells. We have determined that this antibody specifically detects essentially all MUC1 species when used in western blot analysis, visualization of the MUC1 receptor on the surface of cells either free in solution or in a tissue specimen, and the like. The inventors have also produced an antibody against the var-PSMGFR (SEQ ID NO: 7) and have demonstrated that this antibody is more specific than the antibody raised against the native sequence for probing cells, tissue specimens, for use in western blots, and in other analytical methods where the aim is to detect all the MUC1 expressed on cell surfaces. Antibodies raised against the truncated var-PSMGFR (SEQ ID NO: 6) may also be effective for probing cells, tissue specimens,

for use in western blots, and in other analytical methods where the aim is to detect all the MUC1 expressed on cell surfaces.

The inventors have demonstrated that antibodies directed against a portion or portions of the IBR can be useful for detecting the presence of the tumor-related cleavage products PSMGFR and TSESMGFR, which would be left attached to the cell surface and which function as growth factor receptors to increase tumor development and cancer progression. These antibodies used singly or in combinations can provide information regarding the aggressiveness of the patient's cancer and can be useful for probing samples derived from bodily fluids as well as samples involving cells and tissue. A determination of cancer aggressiveness may be made by using combinations of antibodies and thereby determining the ratio of cleaved receptor to uncleaved receptor. Combinations of antibodies that recognize different portions of the MUC1 receptor may be used to determine which portions and relative amounts of the MUC1 receptor are present on the cell surface or in the circulation as a method to diagnose, characterize, assess metastatic potential, design therapeutic protocols and track the patient's response to those therapies.

Agents that have a signaling capability, e.g. antibodies, cognate proteins, or small molecules, that bind to a portion or portions of the ESPSMGFR are useful, in certain embodiments, as diagnostic agents to detect whether or not a cell, tissue specimen or other sample presents a MUC1 species that promotes cell proliferation. Other agents, e.g. antibodies, that bind to the PSMGFR and that have a signaling capability are preferred, in certain embodiments, as diagnostic agents to detect whether or not a cell, tissue specimen or other sample presents a MUC1 species that promotes cell proliferation. Antibodies that bind to the PSMGFR portion are preferred, in certain embodiments, as diagnostic tools for determining whether a cancer is MUC1-positive or negative because these antibodies are capable of recognizing MUC1 in the cleaved or uncleaved state. The use of antibodies that recognize the N-terminal half of the IBR used in combination with an antibody that recognizes the UR are, in certain embodiments, useful for diagnosing MUC1-positive cancers wherein the sample is derived from a patient's bodily fluid. High levels of IBR that has been released from

the cell surface is indicative of cancer and particularly high levels are indicative of an aggressive cancer.

Patient specimens that are analyzed to determine the presence of, or the cancerous potential of, the MUC1 receptor, according to certain embodiments of the invention, may include tumor specimens, tissue specimens, needle biopsy material, 5 cells extracted from a blood sample, the shed portion of the MUC1 receptor in a blood sample or other bodily fluids including breast milk, or MUC1-associated factors, such as ligands and modifying ligands in the blood and in other specimens.

In certain embodiments, a tumor is excised from a patient and analyzed to 10 determine whether or not it is cancerous. It is then characterized as to whether or not it expresses MUC1 by treating the specimen with an antibody directed against PSMGFR (SEQ. ID No. 36). Visual inspection is made to determine whether or not the expressed MUC1 is clustered or is expressed over the entire cell surface, which is characteristic of MUC1-associated cancers. The levels of PSMGFR that are expressed on cells is 15 compared to established levels that would normally be present on healthy MUC1-positive cells. High levels of MUC1 species that interact with anti-PSMGFR are an indication of cancer and its aggressive potential. In certain embodiments the specimen is probed with anti- PSMGFR and an antibody that recognizes the unique region, and the ratio of PSMGFR reactivity to anti-unique region reactivity is calculated. A high 20 ratio of PSMGFR unique region, i.e. more cleaved MUC1 is present than uncleaved MUC1 indicates an aggressive cancer and thus this measurement is used for prognosis and to design appropriate therapies. If the specimen is determined to be cancerous and expresses MUC1, the condition is treated with a compound that directly binds to the PSMGFR portion of the receptor, such as compounds from Tables 2, 3, 4, and 5, for 25 example compounds Nos. 173 and/or 96.

The present invention also involves, in one aspect, methods for treating patients susceptible to or exhibiting symptoms of a tumorigenic condition or a condition where healthy receptor clustering has been disrupted.

The present invention also provides for the treatment of patients for a condition 30 different from cancer, including conditions that can be unrelated to cancer, in some embodiments of the present invention. If a composition of the invention is known for

treatment of a different condition, the present invention also involves use of that composition for treatment of cancer where indicated. The present invention, in certain embodiments, also includes treatments where the dosage, delivery technique or vehicle, combination with other pharmaceutical compositions or lack of combination with other pharmaceutical compositions, rate of administration, timing of administration, or other factor differs from the use of the composition for treatment of the condition different from cancer.

In another set of embodiments, the invention is directed to treating a patient population never before treated with drugs useful according to certain methods of the invention, including patients who are not suffering from or indicating susceptibility to abnormal cell proliferation, cancers or tumors, particularly MUC1-associated cancers. In other words, the treatment preferably is directed to patient populations that otherwise are free of symptoms that call for treatment with any of the drugs useful according to the invention.

International patent application serial number PCT/US01/12484, filed 04/12/01 by Bamdad *et al.*, entitled "Treatment of Neurodegenerative Disease" (International patent publication WO 01/78709, published October 25, 2001), International patent application serial number PCT/US00/01997, filed 01/25/00 by Bamdad *et al.*, entitled "Rapid and Sensitive Detection of Aberrant Protein Aggregation in Neurodegenerative Diseases" (International patent publication WO 00/43791, published July 27, 2000), and International patent application serial number PCT/US00/01504, filed 01/21/00 by Bamdad, *et al.*, entitled "Interaction of Colloid-Immobilized Species with Species on Non-Colloidal Structures" (International patent publication WO 00/34783, published July 27, 2000), all are incorporated herein by reference. Also incorporated herein by reference are the following: International patent application serial no. PCT/US01/44782, filed 11/27/01, publication WO 02/056022, published 07/18/02, entitled "Diagnostic Tumor Markers, Drug Screening for Tumorigenesis Inhibition, and Compositions and Methods for Treatment of Cancer", by Bamdad, *et al.*, U.S. patent application serial no. 09/631,818, filed 08/03/00, entitled "Rapid and Sensitive Detection of Protein Aggregation"; U.S. provisional patent application serial no. 60/213,763, filed 06/23/00, entitled "Detection of Binding Species with Colloidal and

Non-Colloidal Structures”; U.S. provisional patent application 60/248,866 by Bamdad, *et al.*, filed 11/15/00, entitled “Detection of Binding Species with Colloidal and Non-Colloidal Structures”; U.S. provisional patent application 60/248,865 by Bamdad, *et al.*, filed 11/15/00, entitled “Endostatin-Like Angiogenesis Inhibition”; U.S.

- 5 Provisional Patent Application 60/317,302, filed September 5, 2001, entitled “Compositions and Methods of Treatment of Cancer,” by C. Bamdad, *et al.*; and U.S. Provisional Patent Application 60/376,732, filed May 1, 2002, entitled “Compositions and Methods of Treatment of Cancer,” by C. Bamdad, *et al*

The present invention, in certain embodiments, involves compositions related to
10 cancers and methods of treatment of cancers characterized by the aberrant expression of a class of cell surface receptors characterized by interchain binding regions. One such set of cancers are those cancers characterized by the aberrant expression of MUC1. Much of the description of the invention herein involves cells that aberrantly express MUC1. It is to be understood that in these instances the description is to be considered
15 exemplary, and that the principles of the invention apply to other cell surface receptors that function by a similar mechanism. With the disclosure herein, those of ordinary skill in the art will readily be able to identify other cell surface receptors that function by this or a similar mechanism, and to apply the invention to those cancers characterized by aberrant expression of those receptors. The invention is based on a
20 novel mechanism involving aberrant expression of cell surface receptors, exemplified by MUC1, which was elucidated by the inventors.

One aspect of the invention is directed to a method for treating a subject diagnosed or at risk of cancer or tumor characterized by the aberrant expression of MUC1. The treatments of the present invention involve the use of compositions or
25 “agents” as described herein. That is, one aspect of the invention involves a series of compositions or agents useful for treatment of cancer or tumor characterized by the aberrant expression of MUC1. These compositions may also be packaged in kits, optionally including instructions for use of the composition for the treatment of such conditions. These and other embodiments of the invention may also involve promotion
30 of the treatment of cancer or tumor according to any of the techniques and compositions and combinations of compositions described herein.

One aspect of the invention provides a pharmaceutical preparation comprising a composition comprising any of compositions shown below (numbered 1-183), optionally with a pharmaceutically active carrier:

In one embodiment, the composition comprises homologs, analogs, derivatives, enantiomers and functionally equivalent compositions thereof of compositions 1-183. Another aspect of the present invention provides any of the above-mentioned compositions as being useful for the treatment of cancer and particularly MUC1-associated cancers. In one embodiment, compositions are compositions Compound Nos. 173 and/or 96.

In one aspect, the invention is defined, at least in part, by compositions having certain structures, as further described below. In these structures, the term "chemical bond" refers to any type of chemical bond, for example, a covalent bond, an ionic bond, a hydrogen bond, a van der Waals bond, a metal ligand bond, a dative bond, a hydrophobic interaction, or the like. It is to be understood that all compositions are useful or potentially useful for any of the methods of treatment described herein.

In these structures, atoms able to form at least three covalent bonds include those atoms of the carbon family (e.g., carbon, silicon, or germanium), the nitrogen family (e.g., nitrogen, phosphorus, or arsenic), or the boron family (e.g., boron, aluminum, or gallium). In some embodiments, the atoms able to form at least three covalent bonds found within structures of the invention are carbon, nitrogen, silicon, and phosphorus, and in certain embodiments, the atoms are carbon and nitrogen.

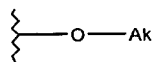
The term "halogen," or equivalently, "halogen atom," is given its ordinary meaning as used in the field of chemistry. The halogens include fluorine, chlorine, bromine, iodine, and astatine. Preferably, the halogen atoms used in the present invention include one or more of fluorine, chlorine, bromine, or iodine. In certain embodiments of the invention, the halogen atoms found within the structure are fluorine, chlorine, and bromine; fluorine and chlorine; chlorine and bromine, or a single type of halogen atom.

As used herein, a "saturated" bond is given its ordinary meaning as used in the field of chemistry. A saturated moiety generally does not contain any double, triple, or higher order chemical bonds in its structure. The saturated moiety can contain any

number or types of atoms (e.g., oxygen, carbon, nitrogen, hydrogen, or halogen atoms) in any configuration, so long as the moiety contains only single bonds between the atoms. For example, the saturated moiety may be an aliphatic structure or a cyclic structure. A saturated moiety may be connected to a parent structure at one or more
5 points. Examples of saturated moieties include:

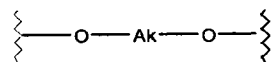


or



10

which each are connected to a parent structure at one point, or:



15

which is connected to a parent structure at more than one point (in this example, using ether linkages). In these structures, "Ak" refers to an alkyl group, as described below. As one example, the alkyl group in these structures may have one, two, three, or four carbon atoms, and may be straight-chained or branched, as long as no double or triple
20 bonds are present. The alkyl group may also include only hydrogen atoms, or include halogen atoms as well.

Conversely, an "unsaturated" moiety is a moiety that contains at least one higher-order chemical bond within its structure, i.e., at least one double bond or triple bond between two atoms within its structure. The unsaturated moiety may contain, in
25 some cases, more than one double and/or triple bond within its structure, for example, as in an alkadiene or an alkenyne.

As used herein, an "alkyl" is given its ordinary meaning as used in the field of organic chemistry. Alkyl or aliphatic groups typically contains any number of carbon atoms, for example, between 1 and 20 carbon atoms, between 1 and 15 carbon atoms,

between 1 and 10 carbon atoms, or between 1 and 5 carbon atoms. In some embodiments, the alkyl group will contain at least 1 carbon atom, at least 2 carbon atoms, at least 3 carbon atoms, at least 4 carbon atoms, at least 5 carbon atoms, at least 6 carbon atoms, at least 7 carbon atoms, or at least 8 carbon atoms. Typically, an alkyl group is a non-cyclic structure. In certain embodiments, the alkyl group is a methyl group or an ethyl group.

The carbon atoms may be arranged in any configuration within the alkyl moiety, for example, as a straight chain (i.e., a *n*-alkyl such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, or undecyl) or a branched chain, for example, a *t*-butyl group, or an isoalkyl group such as isopropyl, isobutyl, isopentyl, or isohexyl. The alkyl moiety may contain none or any number of double or triple bonds within its structure, for example, as in an alkene, an alkyne, an alkadiene, an alkadiyne, an alkenyne, etc.

The alkyl group may contain any number of substituents. For example, the alkyl group may contain a halogen, an alkoxy (e.g., a methoxy, an ethoxy, a propoxy, an isopropoxy, a butoxy, a pentoxy, or the like), an amine (e.g., a primary, secondary, or tertiary amine, for example, an dimethylamine ethyl group), or a hydroxide as a substituent. As one example, if the alkyl group is a methyl group, then the methyl group may be substituted to form, for instance, a halogenated methyl group such as chloromethyl, bromomethyl, or iodomethyl. In some embodiments of the invention, more than one substituent may be present. For example, the alkyl group may have two or more halogen atoms (for example, two chlorine atoms, or a chlorine and a bromine atom), a halogen and an alkoxy group, or the like.

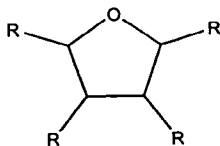
In some embodiments of the invention, the alkyl group may also contain one or more heteroatoms substituted within the alkyl group, such as a nitrogen atom (e.g., as in an amine such as a primary, secondary, or tertiary amine) or an oxygen atom (as in an ether moiety). However, in other embodiments of the invention, the main chain of the alkyl group is free of heteroatoms and includes carbon atoms. As used herein, the term "heteroatoms" refers to atoms that can replace carbon atoms within an alkyl group without affecting the connectivity of the alkyl group; these typically include oxygen and nitrogen atoms. Halogen atoms and hydrogen atoms are not considered to be

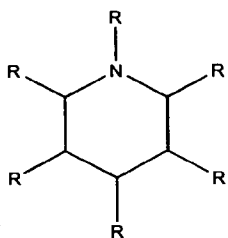
heteroatoms; for example, a chlorine atom can replace a hydrogen atom within an alkyl group without affecting the connectivity of the alkyl group. As used herein, a "non-heteroatom alkyl group" is an alkyl group which does not contain any atoms at the carbon positions other than carbon. Some structures are defined as being free of non-terminal heteroatoms. As used herein, a "non-terminal" atom is an atom within a structure that is connected to at least two different atoms having a valency greater than 1 (e.g., the atom is connected to two non-hydrogen and non-halogen atoms). For example, the oxygen in $\text{-CH}_2\text{-OH}$ and the nitrogen atom in $\text{-CH}_2\text{-NH}_2$ are not connected to two different atoms having a valency greater than 1, and thus are not non-terminal heteroatoms.

Similarly, a "cyclic" structure, as used herein, is given its ordinary definition in the field of organic chemistry, i.e., a structure that contains at least one ring of atoms, and may contain more than one ring of atoms. In other words, a cyclic structure has at least one chain of atoms that does not have a terminal end. The chain may have, for example, three, four, five, six, seven, or more atoms arranged to form a ring. The atoms within the chain may be carbon atoms, nitrogen atoms, oxygen atoms, silicon atoms, or any other atom that is able to bond to at least two different atoms.

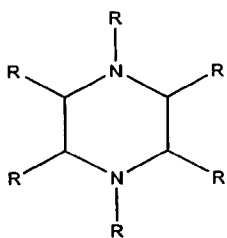
In some embodiments of the invention, one or more substituents may be present on the cyclic structure. The substituents may be any substituent, as previously described in connection with alkyl moieties, for example, a halogen, an alkoxy, an amine, a hydroxide, or the like. In some embodiments, the substituents may also be alkyl groups, as previously described, for example, a methyl group, an ethyl group, a propyl group, and the like.

The cyclic structure may have one or more heteroatoms in some embodiments. For example, the cyclic structure may include a cyclohexane or a cyclopentane ring having one or more heteroatoms, such as:





or



5

where the R's indicate the presence of additional atoms or substituents. The atoms substituted within the cyclohexane ring are able to form at least three covalent bonds, and, if able to form four covalent bonds, the fourth covalent bond may be attached to any atom.

10

The cyclic structure may be a saturated cyclic structure (such as a cyclohexyl or a cyclopentyl structure), or an unsaturated cyclic structure (such as a cyclohexenyl structure or an aromatic structure). Examples of aromatic structures, include, for instance, phenyl, naphthalenyl, anthacenyl, tolyl, pyridinyl, furanyl, pyrrolyl, and the like. A "nonaromatic cyclic structure" is a structure in which aromaticity of the cyclic structure is not present (for example, as in a saturated cyclic structure, a cycloalkenyl moiety, etc.)

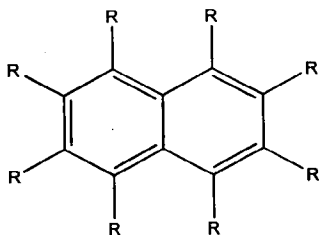
15

In one set of embodiments, the aromatic structure includes a benzene ring. If substituents are present on the benzene ring (as previously discussed, for example, a halogen atom, a methyl group, a methoxy group, a trifluoromethyl group, etc.), they may be located in any position, i.e., in any *ortho*, *meta*, or *para* position, relative to the point of attachment of the benzene ring. If more than one substituent is present, then the substituents may be located at any available point within the benzene ring. For

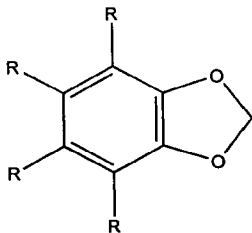
20

example, if there are two substituents, they may be located in the *ortho* and *meta* positions (i.e., in the 2,3 or 2,5 positions), the *ortho* and *para* positions, in the two *ortho* positions, in the two *meta* positions, or in the *meta* and *para* positions.

In one set of embodiments, the aromatic group is a nonsubstituted aromatic group, for example, a phenyl or a naphthalenyl group. In another set of embodiments, the aromatic structure is a halophenyl group or a dihalophenyl group, for example, 3-chloro-4-fluorophenyl; *o*-, *m*-, or *p*-chlorophenyl; 2,4-difluorophenyl; or *o*-, *m*-, or *p*-bromophenyl. In another set of embodiments, the aromatic structure is a methylphenyl or a dimethyl phenyl group, for example, *o*-, *m*-, or *p*-methylphenyl; 2,3-dimethylphenyl; 2,4-dimethylphenyl; 2,5-dimethylphenyl. In another set of embodiments, the aromatic group is an alkylphenyl group, such as *o*-, *m*-, or *p*-methylphenyl; *o*-, *m*-, or *p*-ethylphenyl; 2-phenylethyl, or benzyl. In another set of embodiments, the aromatic structure is a halomethylphenyl group, such as 3-chloro-2-methylphenyl. In another set of embodiments, the aromatic structure is an alkoxyphenyl or a dialkoxyphenyl group, for example, *o*-, *m*-, or *p*-isopropoxyphenyl; *o*-, *m*-, or *p*-methoxyphenyl; *o*-, *m*-, or *p*-ethoxyphenyl; or 2,4-dimethoxyphenyl. In one set of embodiments, the aromatic group is fused with another ring of atoms. The second ring may be aromatic or nonaromatic. Examples include:



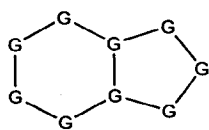
20 and



where the R's indicate the presence of additional atoms or substituents.

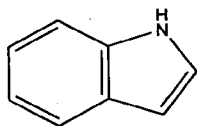
If the cyclic structure has more than one ring of atoms, the rings may be distributed in any manner within the moiety. For example, the two rings may not share a common atom, share only one common atom (e.g., as in a spiro- structure), or share more than one atom, as in a bicyclic structure or a propellane structure. If the two
5 rings share at least one common chemical bond between two atoms, then the rings may be considered to be "fused."

One example of a fused ring system is a structure:



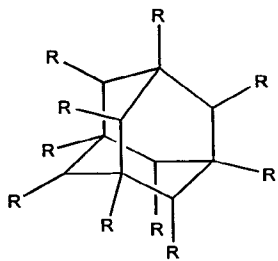
10

where a five member ring is fused to a six member ring in a bicyclic arrangement, and G represents atoms each having at least three covalent bonds, as previously discussed. In some embodiments, one or both rings may be aromatic. As one example, a single
15 nitrogen substitution onto the five-member ring, when both rings are aromatic, can result in an indole moiety, for example:



20 Additionally, other substituents or cyclic rings may be substituted onto the structure as well, for example, a cyclohexyl moiety.

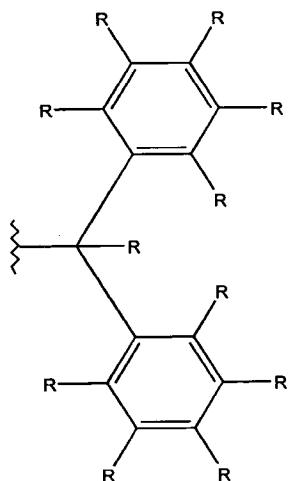
If several rings are jointly fused to each other, then the rings may be considered to be "multifused." One example of a multifused compound is an adamantane structure:



where the R's indicate the presence of additional atoms or substituents.

As used herein, when two cyclic groups are in a "branched configuration," the two cyclic groups are on different branches of a common moiety. In other words, the two cyclic groups are not serially arranged relative to each other. That is, removal of either of the cyclic structures within the moiety does not automatically cause the other cyclic structure to be disconnected from the rest of the moiety. One example of this is illustrated by a diphenylmethyl moiety:

10



where the R's indicate the presence of additional atoms or substituents.

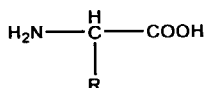
In one set of embodiments, the composition includes a substituted urea moiety. The substituted urea moiety includes at least one cyclic structure having at least seven members. In some cases, the cyclic structure may be a substituted cyclic structure, for example, the structure may include an azepane moiety or a cycloheptane structure, or

15

the structure may include a cycloalkone moiety, that is, an oxygen atom that is double bonded to a member of the cyclic ring.

An "amino acid" is given its ordinary meaning as used in the field of biochemistry. An amino acid typically has a structure:

5



In this structure, R may be any suitable moiety. For example, R may be a hydrogen atom, a methyl group, or an isopropyl group. As used herein, the "natural amino acids" are the 20 amino acids commonly found in nature, i.e., alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. Similarly, an unnatural amino acid is an amino acid, where the R group does not correspond to one of the natural amino acids.

15 In one embodiment, the compositions further comprise homologs, analogs, derivatives, enantiomers and functionally equivalent compositions thereof of the compositions of the invention, for example, compositions 1-183. Such homologs, analogs, derivatives, enantiomers and functionally equivalent compositions thereof of the compositions may be used in any of the assays and/or treatment protocols described herein that are able to detect or treat cancer, particularly MUC1-associated cancers. "Functionally equivalent" generally refers to a composition capable of treatment of patients having MUC1-associated cancer, or of patients susceptible to MUC1-associated cancers. It will be understood that the skilled artisan will be able to manipulate the conditions in a manner to prepare such homologs, analogs, derivatives, enantiomers and functionally equivalent compositions.

25 Homologs, analogs, derivatives, enantiomers and functionally equivalent compositions which are about as effective or more effective than the parent compound are also intended for use in certain embodiments of the methods of the invention. Such compositions may also be screened by the assays described herein for increased potency and specificity towards the cancer characterized by aberrant expression of

30

MUC1, preferably with limited side effects. Synthesis of such compositions may be accomplished through typical chemical modification methods such as those routinely practiced in the art.

Another aspect of the present invention involves a method comprising providing
5 any of the compositions of the present invention, and performing a combinatorial
synthesis on the composition, preferably to obtain homologs, analogs, derivatives,
enantiomers and functionally equivalent compositions thereof of the composition. An
assay may be performed with the homolog, analog, derivative, enantiomer or
functionally equivalent composition to determine its effectiveness in inhibiting cancer
10 characterized by aberrant expression of MUC1. The combinatorial synthesis can
involve subjecting a plurality of the compositions described herein to combinatorial
synthesis.

Another aspect provides a method of administering any composition of the
present invention to a subject. When administered, the compositions of the invention
15 are applied in pharmaceutically acceptable amounts and as pharmaceutically acceptable
compositions. Such preparations may routinely contain salts, buffering agents,
preservatives, compatible carriers or other therapeutic ingredients. Examples of well-
known carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon,
amylase, natural and modified cellulose, polyacrylamide, agarose and magnetite. The
20 nature of the carrier can be either soluble or insoluble. Those skilled in the art will
know of other suitable carriers, or will be able to ascertain such, using only routine
experimentation.

In some cases, the present invention includes the step of bringing a composition
of the invention into association or contact with a suitable carrier, which may constitute
25 one or more accessory ingredients. The final compositions may be prepared by any
suitable technique, for example, by uniformly and intimately bringing the composition
into association with a liquid carrier, a finely divided solid carrier or both, optionally
with one or more formulation ingredients such as buffers, emulsifiers, diluents,
excipients, drying agents, antioxidants, preservatives, binding agents, chelating agents,
30 or stabilizers and then, if necessary, shaping the product.

In some embodiments, the compositions of the present invention may be present as a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salts" includes salts of the composition, prepared, for example, with acids or bases, depending on the particular substituents found within the composition and the treatment modality desired. Pharmaceutically acceptable salts can be prepared as alkaline metal salts, such as lithium, sodium, or potassium salts; or as alkaline earth salts, such as beryllium, magnesium or calcium salts. Examples of suitable bases that may be used to form salts include ammonium, or mineral bases such as sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and the like.

Examples of suitable acids that may be used to form salts include inorganic or mineral acids such as hydrochloric, hydrobromic, hydroiodic, hydrofluoric, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, phosphorous acids and the like. Other suitable acids include organic acids, for example, acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, glucuronic, galactunoric, salicylic, formic, naphthalene-2-sulfonic, and the like. Still other suitable acids include amino acids such as arginate, aspartate, glutamate, and the like.

In general, pharmaceutically acceptable carriers for are well-known to those of ordinary skill in the art. As used herein, a "pharmaceutically acceptable carrier" refers to a non-toxic material that does not significantly interfere with the effectiveness of the biological activity of the active ingredient or ingredients. Pharmaceutically acceptable carriers include, for example, diluents, emulsifiers, fillers, salts, buffers, excipients, drying agents, antioxidants, preservatives, binding agents, bulking agents, chelating agents, stabilizers, solubilizers, and other materials well-known in the art. Examples of suitable formulation ingredients include diluents such as calcium carbonate, sodium carbonate, lactose, kaolin, calcium phosphate, or sodium phosphate; granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch, gelatin or acacia; lubricating agents such as magnesium stearate, stearic acid, or talc; time-delay materials such as glycerol monostearate or glycerol distearate; suspending agents such as sodium carboxymethylcellulose, methylcellulose,

hydroxypropylmethylcellulose, sodiumalginate, polyvinylpyrrolidone; dispersing or wetting agents such as lecithin or other naturally-occurring phosphatides; or thickening agents such as cetyl alcohol or beeswax. The compositions of the invention may be formulated into preparations in solid, semi-solid, liquid or gaseous forms such as tablets, capsules, elixrs, powders, granules, ointments, solutions, depositories, inhalants
5 or injectables. The compositions of the present invention may be delivered by any suitable delivery method, for example, oral, parenteral or surgical administration. The invention also embraces locally administering the compositions of the invention, for example, as implants

10 Preparations include sterile aqueous or nonaqueous solutions, suspensions and emulsions. Examples of nonaqueous solvents are propylene glycol, polyethylene glycol, vegetable oil such as olive oil, an injectable organic esters such as ethylolate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride
15 solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, antioxidants, chelating agents and inert gases and the like. Those of skill in the art can readily determine the various parameters for preparing these pharmaceutical
20 compositions without resort to undue experimentation.

The compositions of the invention may be administered singly or in combination with other compositions of the invention or other compositions. For example, in one embodiment, compositions of the invention are administered in
25 combination with agents that block cell surface receptors, such as the alpha-V-beta-3 cell surface receptor.

According to certain embodiments of the methods of the invention, the compositions of the invention can be administered by injection by gradual infusion over time or by any other medically acceptable mode. Any medically acceptable method
30 may be used to administer the composition to the patient. The particular mode selected will depend of course, upon factors such as the particular drug selected, the severity of

the state of the subject being treated, or the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active composition without causing clinically unacceptable adverse effects.

5 The administration may be localized (i.e., to a particular region, physiological system, tissue, organ, or cell type) or systemic, depending on the condition to be treated. For example, the composition may be administered through parental injection, implantation, orally, vaginally, rectally, buccally, pulmonary, topically, nasally, 10 transdermally, surgical administration, or any other method of administration where access to the target by the composition is achieved. Examples of parental modalities that can be used with the invention include intravenous, intradermal, subcutaneous, intracavity, intramuscular, intraperitoneal, epidural, or intrathecal. Examples of implantation modalities include any implantable or injectable drug delivery system. 15 Oral administration may be preferred for some treatments because of the convenience to the patient as well as the dosing schedule. Compositions suitable for oral administration may be presented as discrete units such as capsules, pills, cachettes, tablets, or lozenges, each containing a predetermined amount of the active compound. Other oral compositions include suspensions in aqueous or non-aqueous liquids such as 20 a syrup, an elixir, or an emulsion.

 The compositions of the present invention may be given in dosages, generally, at the maximum amount while avoiding or minimizing any potentially detrimental side effects. The compositions can be administered in effective amounts, alone or in a cocktail with other compounds, for example, other compounds that can be used to treat 25 cancer. An effective amount is generally an amount sufficient to inhibit MUC1-associated cancer within the subject.

 One of skill in the art can determine what an effective amount of the composition is by screening the ability of the composition using any of the assays described herein. The effective amounts will depend, of course, on factors such as the 30 severity of the condition being treated; individual patient parameters including age, physical condition, size and weight; concurrent treatments; the frequency of treatment;

or the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

5 Dosages may be estimated based on the results of experimental models, optionally in combination with the results of assays of the present invention. Generally, daily oral prophylactic doses of active compounds will be from about 0.01 mg/kg per day to 2000 mg/kg per day. Oral doses in the range of 10 to 500 mg/kg, in one or several administrations per day, may yield suitable results. In the event that the
10 response of a particular subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day are also contemplated in some cases to achieve appropriate systemic levels of the composition.

 In administering the compositions of the invention to subjects, dosing amounts,
15 dosing schedules, routes of administration and the like may be selected so as to affect other known activities of these compositions. For example, amounts, dosing schedules and routes of administration may be selected as described herein, whereby therapeutically effective levels for the inhibition or treatment of MUC1-associated cancers are provided, yet therapeutically effective levels for alternative treatments are
20 not provided.

 Other delivery systems suitable for use with the present invention include time-release, delayed release, sustained release, or controlled release delivery systems. Such systems may avoid repeated administrations of the active compounds of the invention in many cases, increasing convenience to the subject and the physician. Many types of
25 release delivery systems are available and known to those of ordinary skill in the art. They include, for example, polymer based systems such as polylactic and/or polyglycolic acid, polyanhydrides, and polycaprolactone; nonpolymer systems that are lipid-based including sterols such as cholesterol, cholesterol esters, and fatty acids or neutral fats such as mono-, di- and triglycerides; hydrogel release systems; silastic
30 systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; or partially fused implants. Specific examples include, but are

not limited to, erosional systems in which the composition is contained in a form within a matrix, or diffusional systems in which an active component controls the release rate. The formulation may be as, for example, microspheres, hydrogels, polymeric reservoirs, cholesterol matrices, or polymeric systems. In some embodiments, the system may allow sustained or controlled release of the active compound to occur, for example, through control of the diffusion or erosion/degradation rate of the formulation. In addition, a pump-based hardware delivery system may be used in some embodiment of the invention.

Use of a long-term release implant may be particularly suitable in some cases.

“Long-term release,” as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the composition for at least 30 or 45 days, and preferably at least 60 or 90 days, or even longer in some cases. Long-term release implants are well known to those of ordinary skill in the art, and include some of the release systems described above.

The present invention also provides any of the above-mentioned compositions useful for treatment of cancer characterized by aberrant expression of MUC1 packaged in kits, optionally including instructions for use of the composition for the treatment of cancer. That is, the kit can include a description of use of the composition for participation in any biological or chemical mechanism disclosed herein associated with cancer or tumor. The kits can further include a description of activity of cancer characterized by aberrant expression of MUC1 in treating the pathology, as opposed to the symptoms of the cancer. That is, the kit can include a description of use of the compositions as discussed herein. The kit also can include instructions for use of a combination of two or more compositions of the invention. Instructions also may be provided for administering the drug by any suitable technique, such as orally, intravenously, directly into the cerebrospinal fluid via a spinal drip, pump or implantable delivery device, or via another known route of drug delivery. Certain embodiments of the invention also involve promotion of the treatment of cancer characterized by aberrant expression of MUC1 according to any of the techniques and compositions and composition combinations described herein.

The compositions of the invention, in some embodiments, may be promoted for treatment of abnormal cell proliferation, cancers, or tumors, particularly MUC1-associated cancers or includes instructions for treatment of accompany cell proliferation, cancers, or tumors, particularly MUC1-associated cancers as mentioned
5 above. In another aspect, the invention provides a method involving promoting the prevention or treatment of cancer via administration of any one of the compositions of the present invention, and homologs, analogs, derivatives, enantiomers and functionally equivalent compositions thereof in which the composition is able to treat MUC1-associated cancers. As used herein, "promoted" includes all methods of doing business
10 including methods of education, hospital and other clinical instruction, pharmaceutical industry activity including pharmaceutical sales, and any advertising or other promotional activity including written, oral and electronic communication of any form, associated with compositions of the invention in connection with treatment of cell proliferation, cancers or tumors. "Instructions" can define a component of promotion,
15 and typically involve written instructions on or associated with packaging of compositions of the invention. Instructions also can include any oral or electronic instructions provided in any manner. The "kit" typically defines a package including any one or a combination of the compositions of the invention and the instructions, or homologs, analogs, derivatives, enantiomers and functionally equivalent compositions
20 thereof, but can also include the composition of the invention and instructions of any form that are provided in connection with the composition in a manner such that a clinical professional will clearly recognize that the instructions are to be associated with the specific composition.

The kits described herein may also contain one or more containers, which can
25 contain compounds such as the species, signaling entities, biomolecules and/or particles as described. The kits also may contain instructions for mixing, diluting, and/or administering the compounds. The kits also can include other containers with one or more solvents, surfactants, preservative and/or diluents (e.g., normal saline (0.9% NaCl), or 5% dextrose) as well as containers for mixing, diluting or administering the
30 components to the sample or to the patient in need of such treatment.

The compositions of the kit may be provided as any suitable form, for example, as liquid solutions or as dried powders. When the composition provided is a dry powder, the powder may be reconstituted by the addition of a suitable solvent, which may also be provided. In embodiments where liquid forms of the composition are used, the liquid form may be concentrated or ready to use. The solvent will depend on the compound and the mode of use or administration. Suitable solvents for drug compositions are well known and are available in the literature. The solvent will depend on the compound and the mode of use or administration.

The kit, in one set of embodiments, may comprise a carrier means being compartmentalized to receive in close confinement one or more container means such as vials, tubes, and the like, each of the container means comprising one of the separate elements to be used in the method. For example, one of the container means may comprise a positive control in the assay. Additionally, the kit may include containers for other components, for example, buffers useful in the assay.

Table 1: Peptide sequences (listed from N-terminus to C-terminus):

Histidine-Tagged Truncated receptor (His-TR) (having "SPY" sequence of var-PSMGFR):

GTINVHDTVETQFNQYKTEAASPYNLTISDVSVSHHHHHH (SEQ ID NO: 1)

An example of a Histidine-Tagged Primary Sequence of the MUC1 Growth Factor Receptor (His-var-PSMGFR) (having "SPY" sequence of var-PSMGFR):

GTINVHDTVETQFNQYKTEAASPYNLTISDVSVSDVPFPFSAQSGAHHHHHHH (SEQ ID NO: 2)

An example of a Histidine-Tagged Primary Sequence of the MUC1 Growth Factor Receptor (His-var-PSMGFR) (having "SPY" sequence of var-PSMGFR) having a single amino acid deletion at the C-terminus of SEQ ID NO: 2):

TINVHDTVETQFNQYKTEAASPYNLTISDVSVSDVPFPFSAQSGAHHHHHHH (SEQ ID NO: 60)

Histidine-Tagged Extended Sequence of MUC1 Growth Factor Receptor (ESMGFR)
(having "SPY" sequence of var-PSMGFR):

VQLTLAFREGTINVHDTVETQFNQYKTEAASPYNLTISDVSVS

5 DVPFPFHSHHHH (SEQ ID NO: 3)

Histidine-Tagged Tumor-Specific Extended Sequence of MUC1 Growth Factor
Receptor (TSESMGFR) (having "SPY" sequence of var-PSMGFR):

SVVVQLTLAFREGTINVHDTVETQFNQYKTEAASPYNLTISDVSVS

10 DVPFPFSAQSGAHHHHH (SEQ ID NO: 61)

Histidine-Tagged Primary Sequence of the Interchain binding Region (His-PSIBR):
HHHHHHGFLGLSNIKFRPGSVVVQLTLAFRE (SEQ ID NO: 4)

15 Histidine-Tagged Truncated Interchain binding Region (His-TPSIBR):
HHHHHHSVVVQLTLAFREG (SEQ ID NO: 62)

Histidine-Tagged Repeat Motif 2 (His-RM2):

PDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTSAHHHHHH (SEQ ID

20 NO: 5)

Truncated PSMGFR receptor (TR) (having "SPY" sequence of var-PSMGFR):
GTINVHDTVETQFNQYKTEAASPYNLTISDVSVS (SEQ ID NO: 6)

25 Native Primary Sequence of the MUC1 Growth Factor Receptor (nat-PSMGFR – An
example of "PSMGFR"):
GTINVHDTVETQFNQYKTEASRYNLTISDVSVSDVPFPFSAQSGA (SEQ ID NO:
36)

Native Primary Sequence of the MUC1 Growth Factor Receptor (nat-PSMGFR – An example of “PSMGFR”), having a single amino acid deletion at the C-terminus of SEQ ID NO: 36):

5 TINVHDTVETQFNQYKTEAASRYNLTISDVSVSDVPPFSAQSGA (SEQ ID NO: 63)

“SPY” functional variant of the native Primary Sequence of the MUC1 Growth Factor Receptor having enhanced stability (var-PSMGFR – An example of “PSMGFR”):

10 GTINVHDTVETQFNQYKTEAASPYNLTISDVSVSDVPPFSAQSGA (SEQ ID NO: 7)

“SPY” functional variant of the native Primary Sequence of the MUC1 Growth Factor Receptor having enhanced stability (var-PSMGFR – An example of “PSMGFR”), having a single amino acid deletion at the C-terminus of SEQ ID NO: 7):

15 TINVHDTVETQFNQYKTEAASPYNLTISDVSVSDVPPFSAQSGA (SEQ ID NO: 64)

Primary Sequence of the Interchain Binding Region) (PSIBR):

20 GFLGLSNIKFRPGSVVVQLTLAFRE (SEQ ID NO: 8)

Truncated Interchain Binding Region) (TPSIBR):

SVVVQLTLAFREG (SEQ ID NO: 65)

Repeat Motif 2 (RM2):

25 PDTRPAPGSTAPPAHGVTSAPDTRPAPGSTAPPAHGV TSA (SEQ ID NO: 9)

Tumor-Specific Extended Sequence of MUC1 Growth Factor Receptor (TSESMGFR) (having “SPY” sequence of var-PSMGFR):

30 SVVVQLTLAFREGTINVHDTVETQFNQYKTEAASPYNLTISDVSVSDVPPFSAQSGA (SEQ ID NO: 66)

Full-length MUC1 Receptor

(Mucin 1 precursor, Genbank Accession number: P15941

MTPGTQSPFF LLLLLTVLTV VTGSGHASST PGGEKETSAT QRSSVPSSTE
KNAVSMTSSV LSSHSPGSGS STTQGQDVTL APATEPASGS AATWGQDVTS
5 VPVTRPALGS TTPPAHDVTS APDNKPAPGS TAPPAHGVTS APDTRPAPGS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS
10 TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
15 APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS
20 TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
TAPPAHGVTS APDTRPAPGS TAPPAHGVTS APDTRPAPGS TAPPAHGVTS
25 VQLTLAFREG TINVHDTVETQ FNQYKTEAAS RYNLTISDVS VSDVPFPFSA
QSGAGVPGWG IALLVLVCVL VALAIVYLIA LAVCQCRRKN YGQLDIFPAR
DTYHPMSEYP TYHTHGRYVP PSSTDRSPYE KVSAGNGGSS LSYTNPAVAA
ASANL

(SEQ ID NO: 10)

A truncated MUC1 receptor isoform having nat-PSMGFR at its N-terminus and including the transmembrane and cytoplasmic sequences of a full-length MUC1 receptor ("nat-PSMGFRTC isoform" - An example of "PSMGFRTC" - shown excluding optional N-terminus signal sequence - SEQ ID NOS: 47, 58, or 59 which
5 may be cleaved after translation and prior to expression of the receptor on the cell surface):

G TINVHDTVETQ FNQYKTEAAS RYNLTISDVS VSDVPFPFSA QSGAGVPGWG
IALLVLCVL VALAIVYLIA LAVCQCRRKN YGQLDIFPAR DTYHPMSEYP
TYHTHGRYVP PSSTDRSPYE KVSAGNGGSS LSYTNPAVAA ASANL
10 (SEQ ID NO: 37)

A truncated MUC1 receptor isoform having nat-PSMGFR and PSIBR at its N-terminus and including the transmembrane and cytoplasmic sequences of a full-length MUC1 receptor ("CM isoform"- shown excluding optional N-terminus signal sequence - S
15 SEQ ID NOS: 47, 58, or 59 which may be cleaved after translation and prior to expression of the receptor on the cell surface):

GFLGLS NIKFRPGSVV VQLTLAFREG TINVHDTVETQ FNQYKTEAAS
RYNLTISDVS VSDVPFPFSA QSGAGVPGWG IALLVLCVL VALAIVYLIA
LAVCQCRRKN YGQLDIFPAR DTYHPMSEYP TYHTHGRYVP PSSTDRSPYE
20 KVSAGNGGSS LSYTNPAVAA ASANL
(SEQ ID NO: 38)

A truncated MUC1 receptor isoform having nat-PSMGFR + PSIBR + Unique Region at its N-terminus and including the transmembrane and cytoplasmic sequences of a full-
25 length MUC1 receptor ("UR isoform"- shown excluding optional N-terminus signal sequences SEQ ID NO: 47, 58, or 59):

ATTPASKSTPFSIPSHHSDTPPTLASHSTKTDASSTHHSTVPPLTSSNHSTSPQLS
TGVSFFFLSFHISNLQFNSSLEDPTDYYQELQRDISEMFLQIYKQGGFLGLSNIK
FRPGSVVVQLTLAFREGTINVHDTVETQFNQYKTEAASRYNLTISDVS VSDVPFP
30 FSAQSGAGVPGWGIALLVLCVLVALAIVYLIALAVCQCRRKNYGQLDIFPAR

DTYHPMSEYPTYHTHGRYVPPSSTD RSPYEKVSAGNGGSSLSYTNPAVAAASANL (SEQ ID NO: 39)

- 5 A truncated MUC1 receptor isoform including the transmembrane and cytoplasmic sequences of a full-length MUC1 receptor (“Y isoform”– shown excluding optional N-terminus signal sequence - SEQ ID NOS: 47, 58, or 59 which may be cleaved after translation and prior to expression of the receptor on the cell surface):
- GSGHASSTPGGEKETSATQRSSVPSSTEKNAFNSSLEDPSTDYYQELQRDISEMFLQIYKQGGFLGLSNIKFRPGSVVVQLTLAFREGTINVHDMETQFNQYKTEAASRYNLTISDVSVDVPPFSAQSGAGVPGWGIALLVLCVLVALAIVYLIALLAVCQCRRKNYGQLDIFPARDTYHPMSEYPTYHTHGRYVPPSSTD RSPYEKVSAGNGGSSLSYTNPAVAATSANL (SEQ ID NO:40)

- 15 A truncated MUC1 receptor isoform having nat-PSMGFR + PSIBR + Unique Region + Repeats at its N-terminus and including the transmembrane and cytoplasmic sequences of a full-length MUC1 receptor (“Rep isoform”– shown excluding optional N-terminus signal sequence - SEQ ID NOS: 47, 58, or 59 which may be cleaved after translation and prior to expression of the receptor on the cell surface):
- 20 LDPRVRTSAPDTRPAPGSTAPQAHGVTS(APDTRPAPGSTAPPAHGVTS)25APDTRPAPGSTAPPAHGVTSAPDNRPALGSTAPPVHNVTASGSASGSASTLVHNGTSARATTTTPASKSTPFPSIPSHHSDTPTTLASHSTKTDASSTHHSSVPPLTSSNHSTSPQLSTGVSFFFLSFHISNLQFNSSLEDPSTDYYQELQRDISEMFLQIYKQGGFLGLSNIKFRPGSVVVQLTLAFREGTINVHDVETQFNQYKTEAASRYNLTISDVSVDVPPFSAQSGAGVPGWGIALLVLCVLVALAIVYLIALLAVCQCRRKNYGQLDIFPARDTYHPMSEYPTYHTHGRYVPPSSTD RSPYEKVSAGNGGSSLSYTNPAVAAASANL (SEQ ID NO: 41)

- 30 N-terminal MUC-1 signaling sequence for directing MUC1 receptor and truncated isoforms to cell membrane surface (optionally present, in whole or part - e.g. up to 3

a.a. may be absent at C-terminal end as indicated by variants in SEQ ID NOS: 47, 58, and 59, at N-terminus of above-listed MUC1 truncated receptor isoforms):

MTPGTQSPFFLLLLLLTVLT (SEQ ID NO: 47).

MTPGTQSPFFLLLLLLTVLT VVTA (SEQ ID NO: 58)

5 MTPGTQSPFFLLLLLLTVLT VVTG (SEQ ID NO: 59)

Proopiomelanocortin (adrenocorticotropin/ beta-lipotropin/ alpha-melanocyte stimulating hormone/ beta-melanocyte stimulating hormone/ beta-endorphin) [Homo sapiens].

10 Accession number: XP_002485

AAAKEGKKSR DRERPPSVPA LREQPPETEP QPAWKMPRSC CSRSGALLA
LLLQASMEVR GWCLESSQCQ DLTTESNLLE CIRACKPDLS AETPMFPGNG
DEQPLTENPR KYVMGHFRWD RFGRNRSSSS GSSGAGQKRE DVSAGEDCGP
15 LPEGGPEPRS DGAKEPGPREG KRSYSMEHFR WGKPVGKKRR PVKVYPNGAE
DESAEAFPLE FKRELTGQRL REGDGPDGPA DDGAGAQADL EHSLLVAAEK
KDEGPYRMEH FRWGSPPKDK RYGGFMTSEK SQTPLVTLFK NAIKNAYKK
GE
(SEQ ID NO: 11)

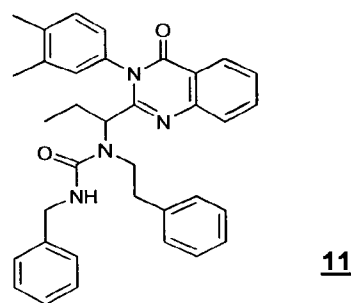
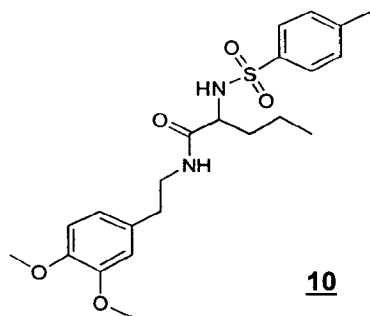
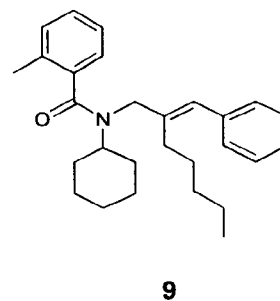
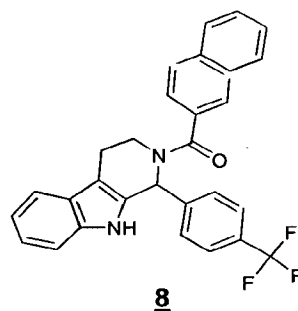
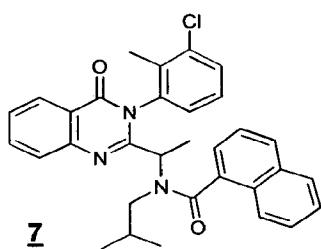
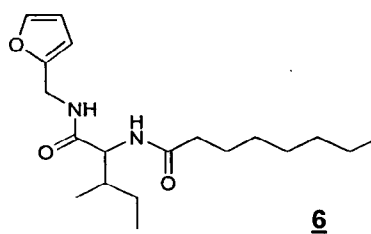
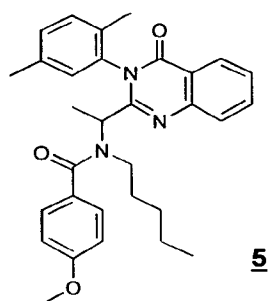
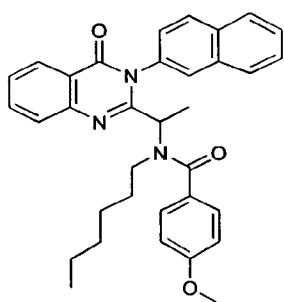
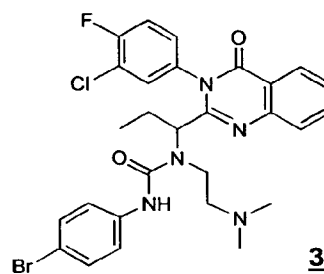
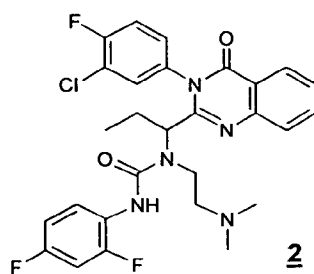
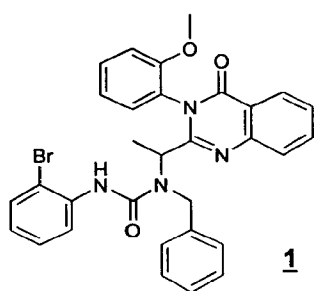
20

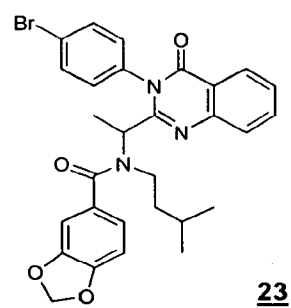
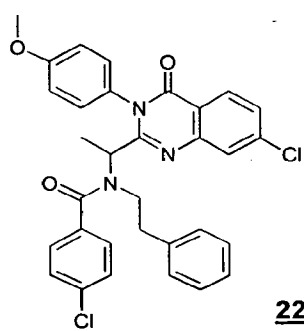
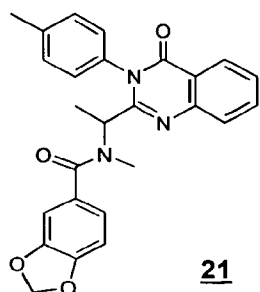
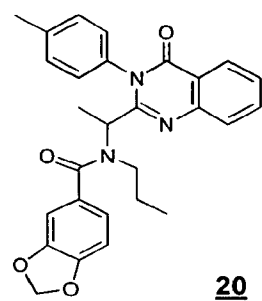
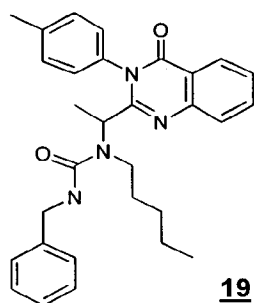
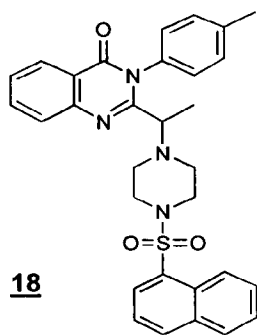
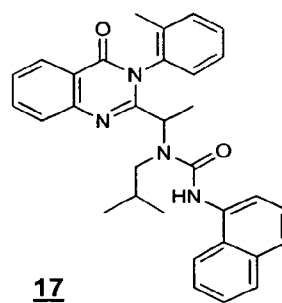
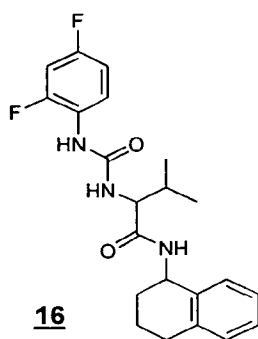
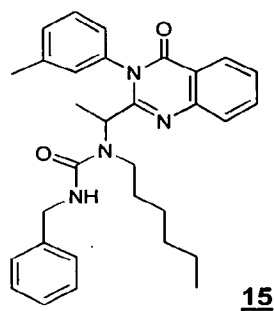
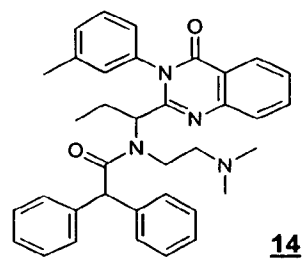
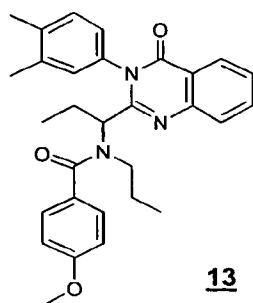
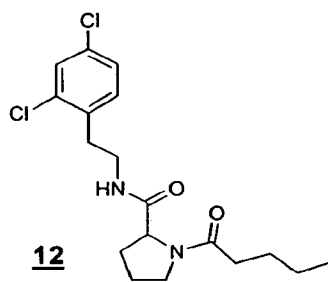
RGD

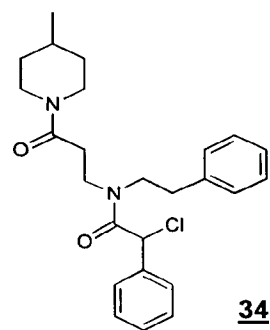
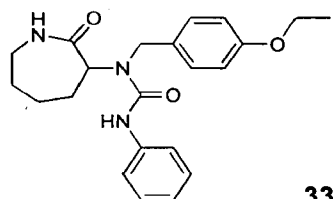
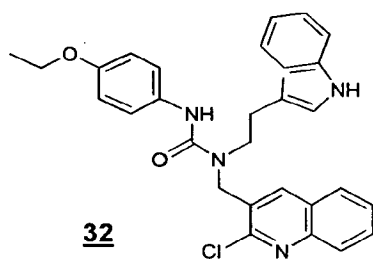
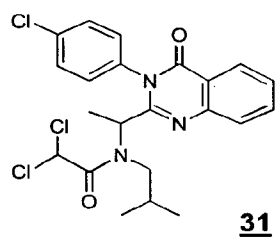
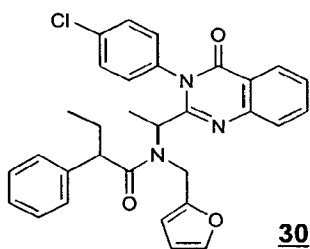
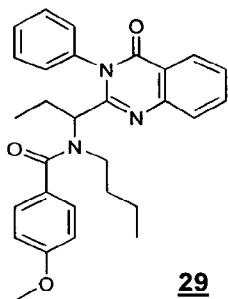
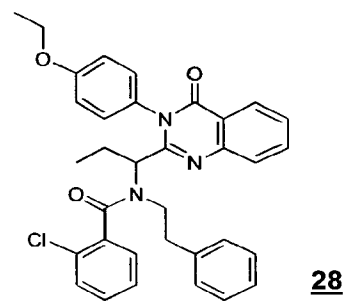
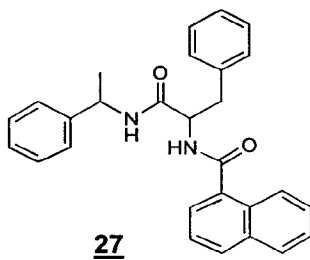
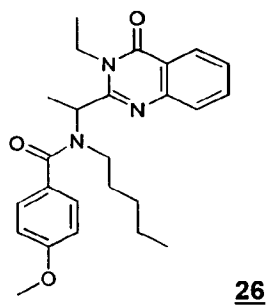
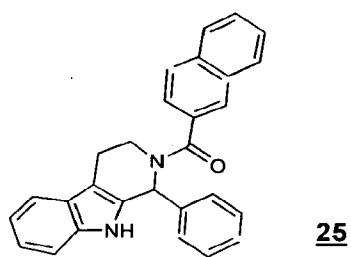
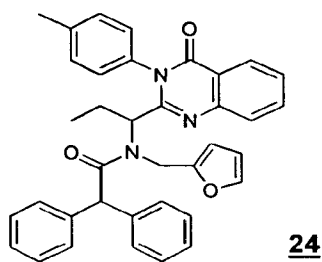
HHHHHHSSSSGSSSSGSSSSGGRGDSGRGDS (SEQ ID NO: 12)

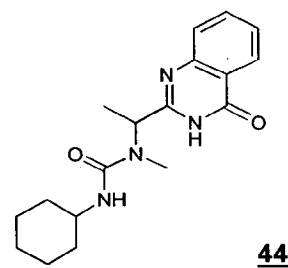
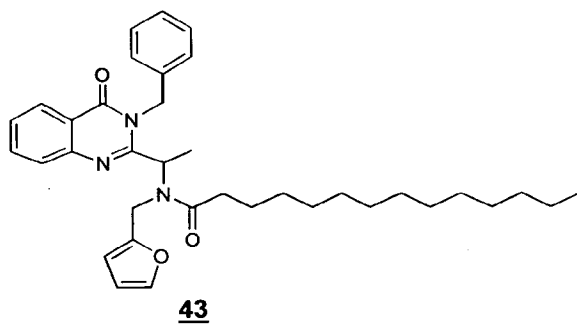
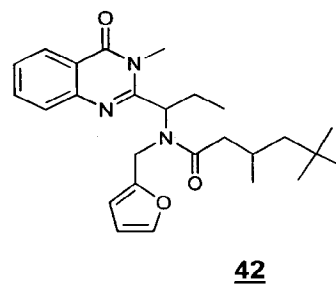
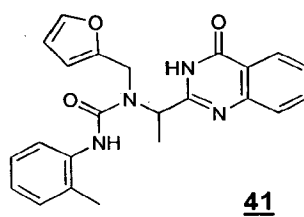
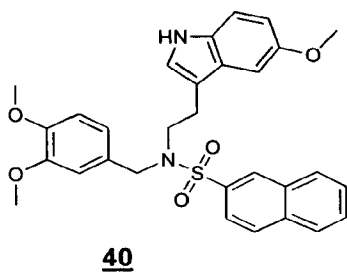
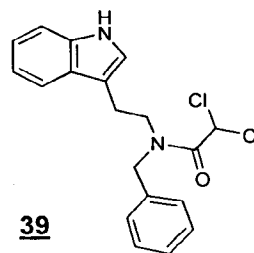
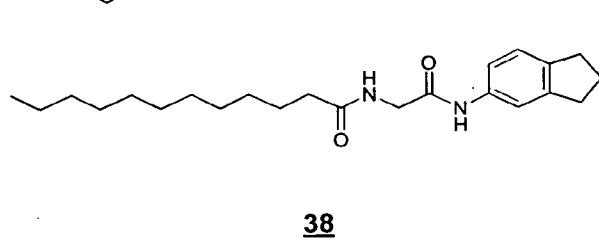
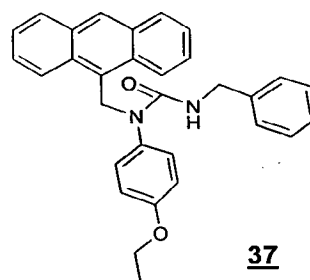
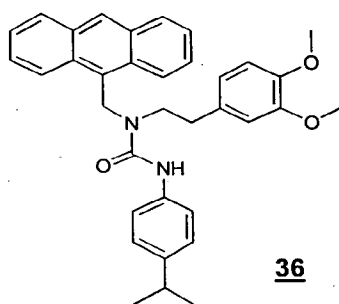
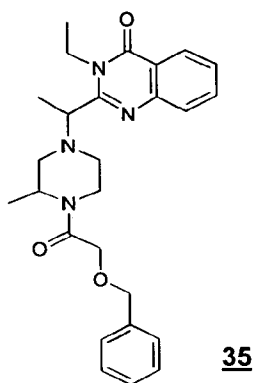
TABLE 2.

25









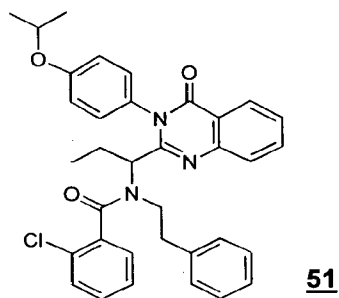
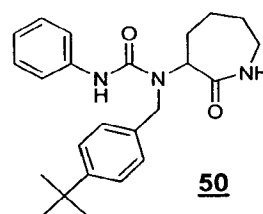
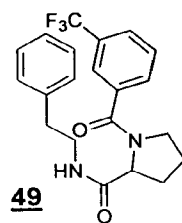
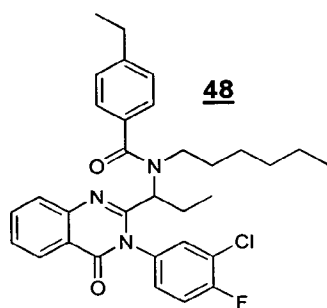
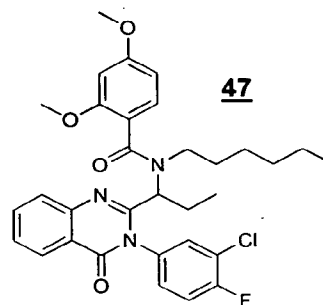
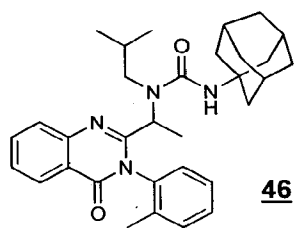
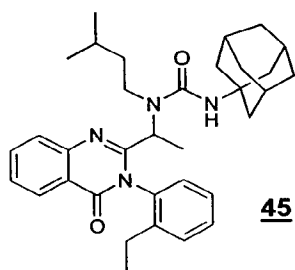
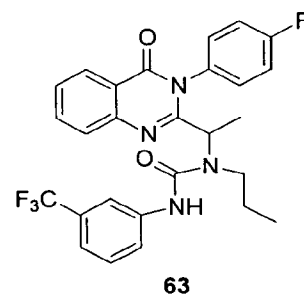
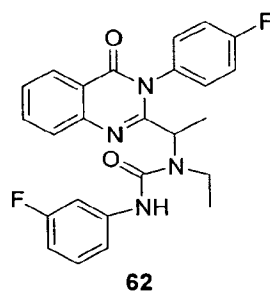
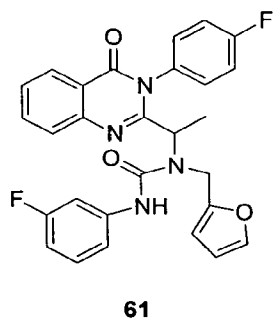
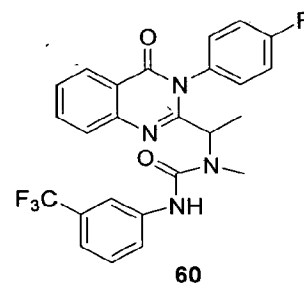
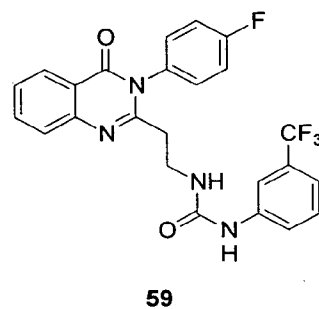
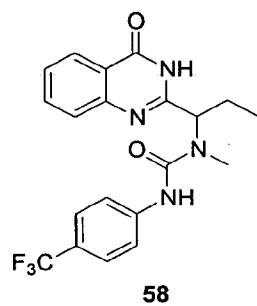
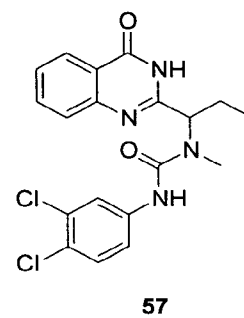
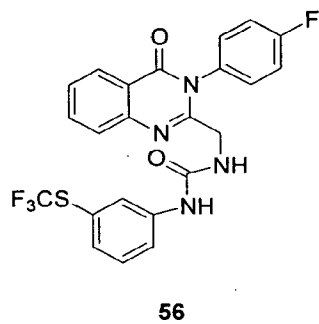
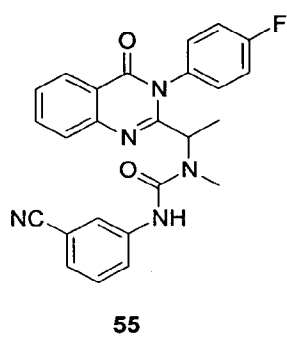
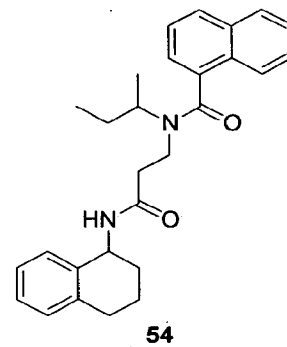
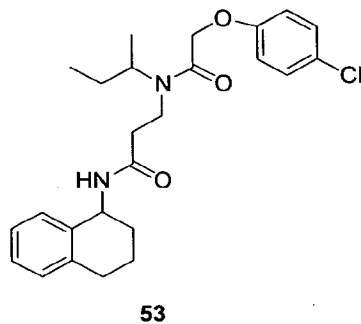
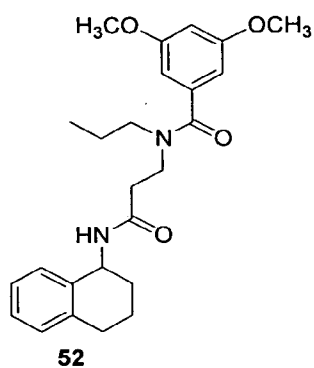
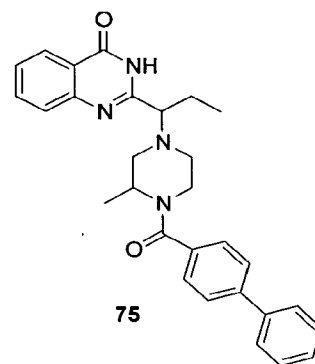
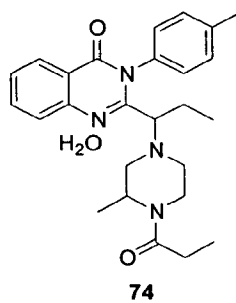
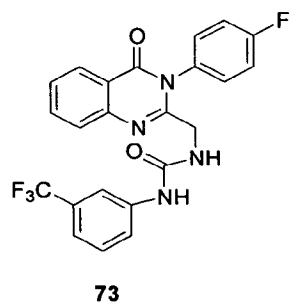
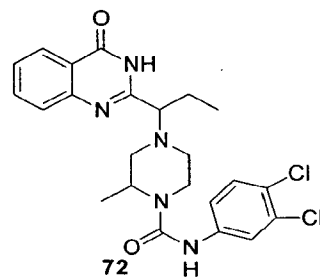
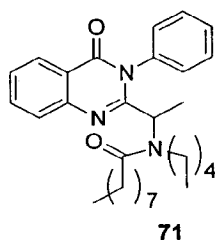
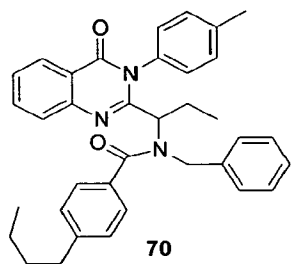
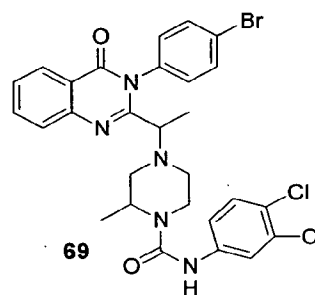
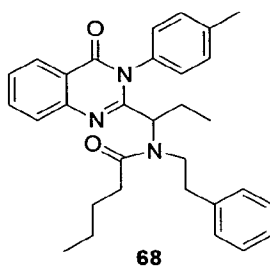
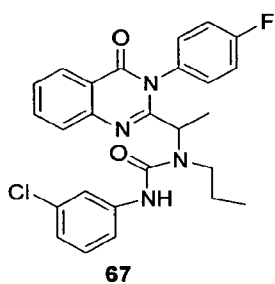
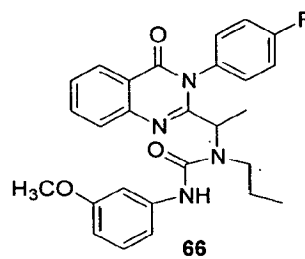
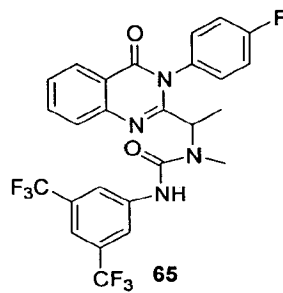
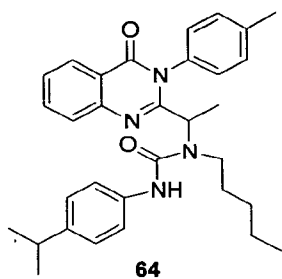
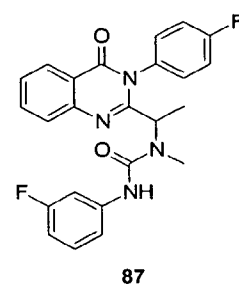
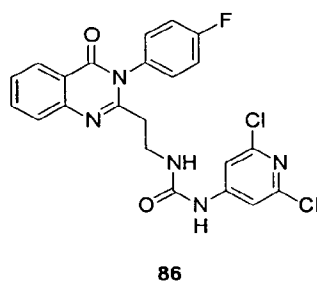
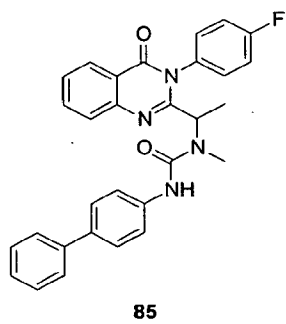
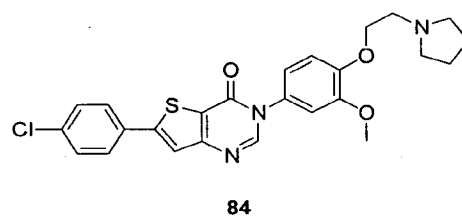
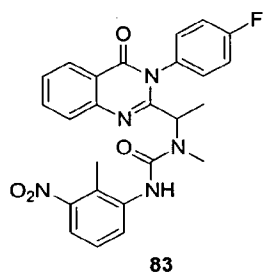
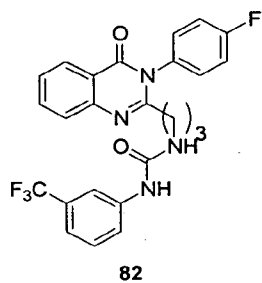
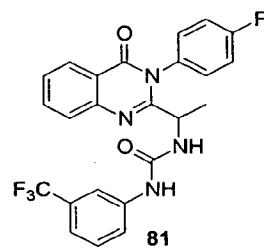
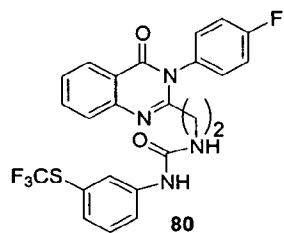
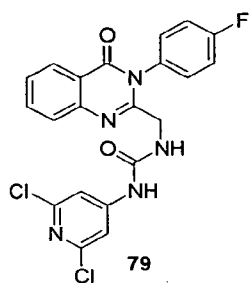
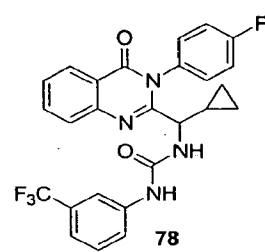
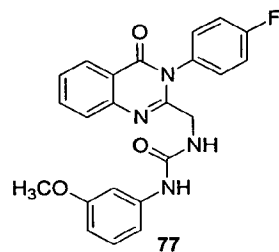
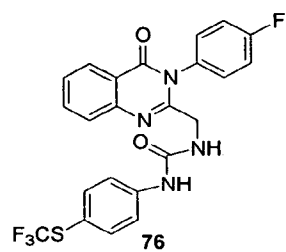
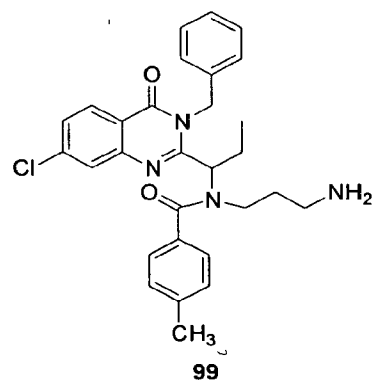
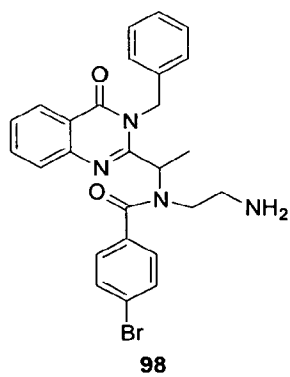
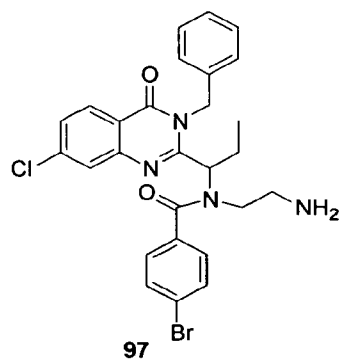
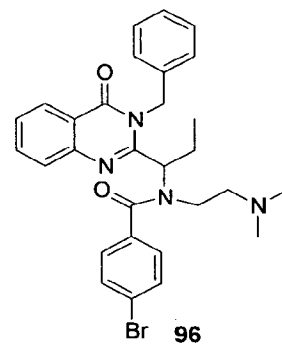
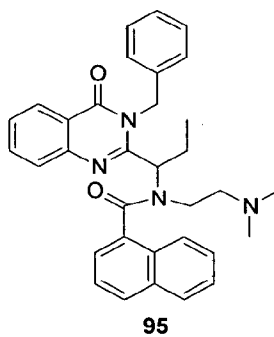
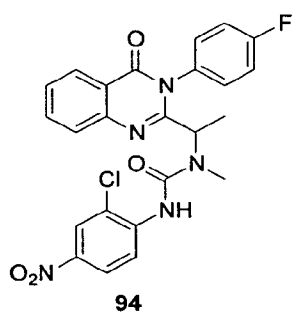
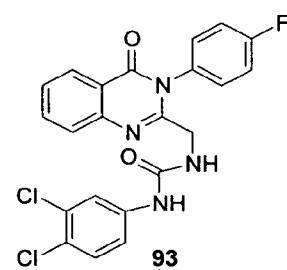
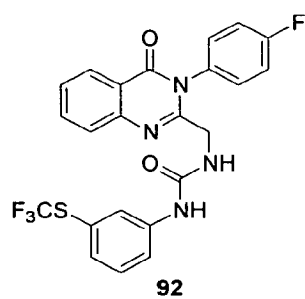
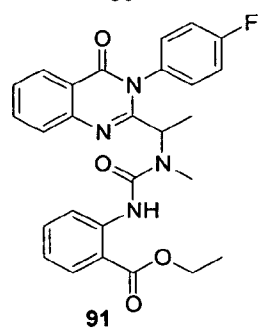
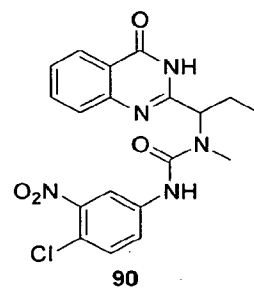
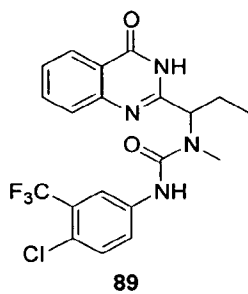
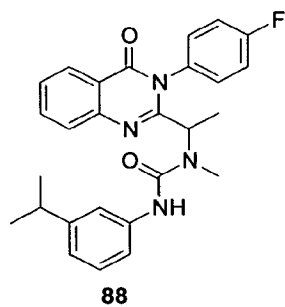


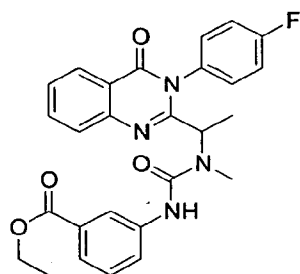
Table 3.



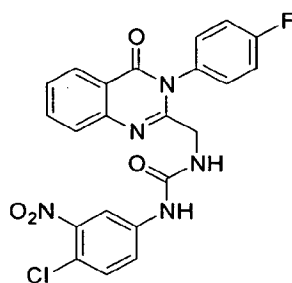




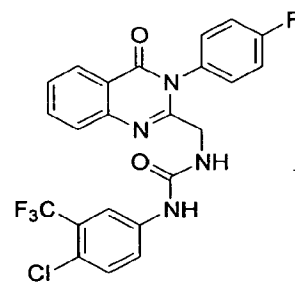




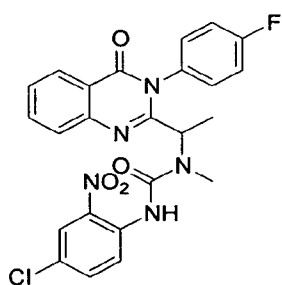
100



101



102



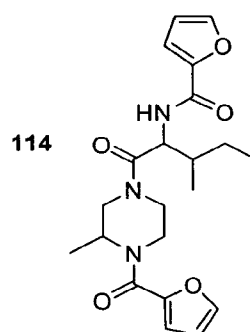
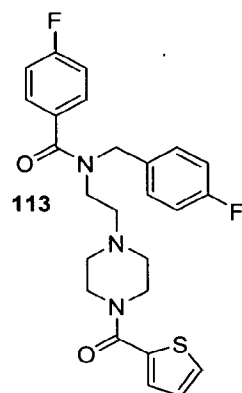
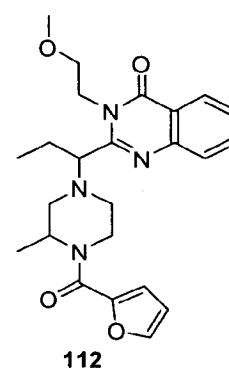
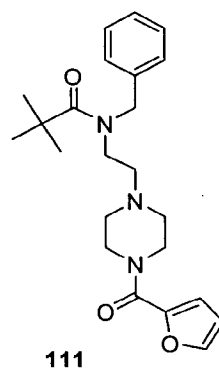
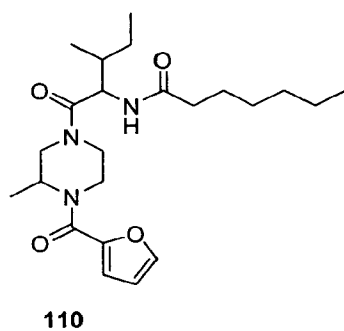
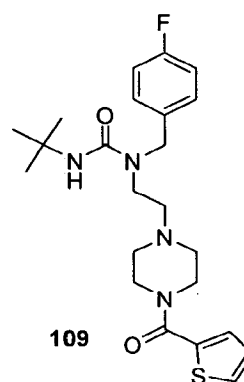
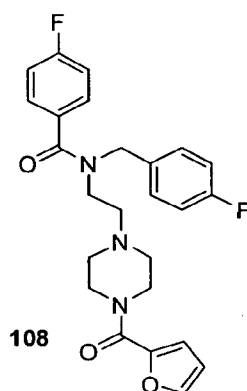
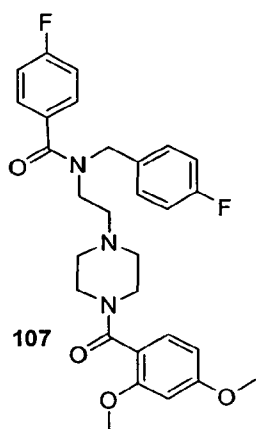
103

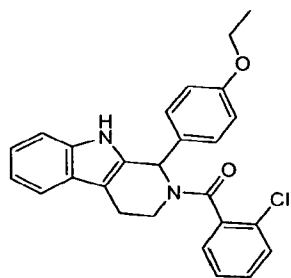
This

Space Intentionally

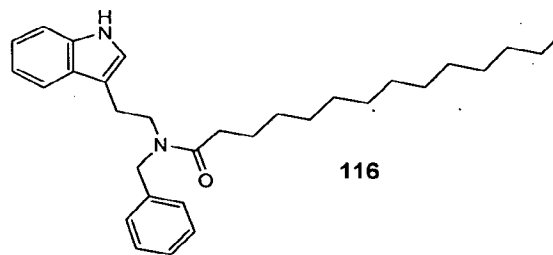
Left Blank

Table 4.

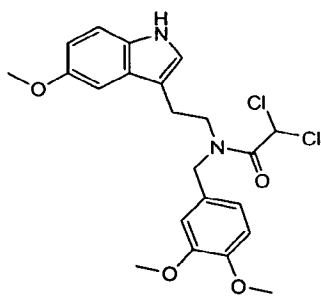




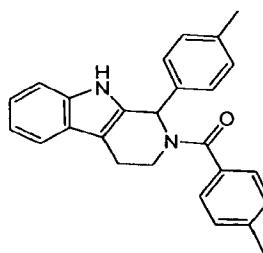
115



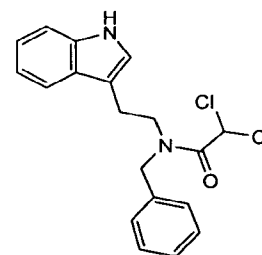
116



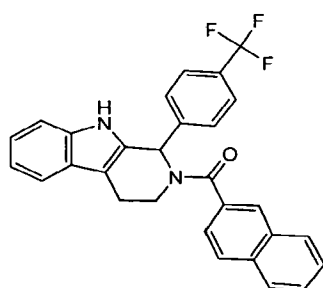
117



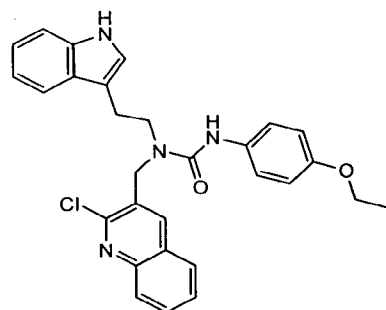
118



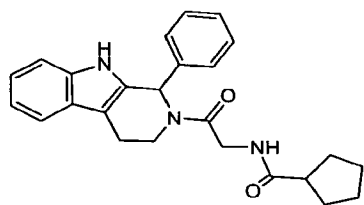
119



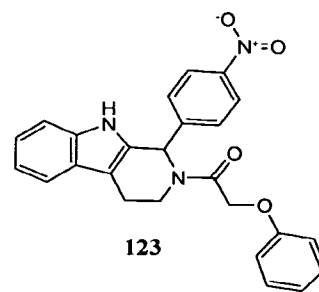
120



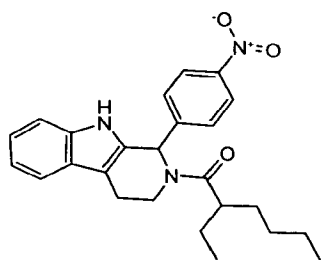
121



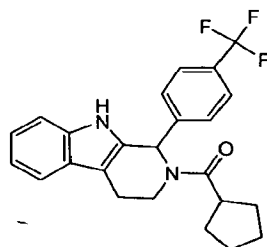
122



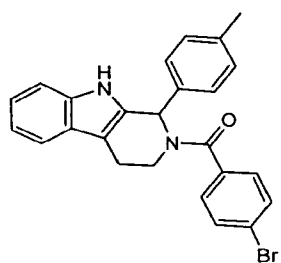
123



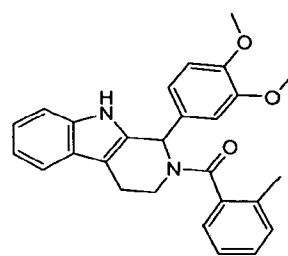
124



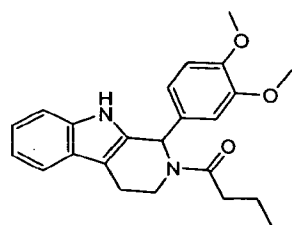
125



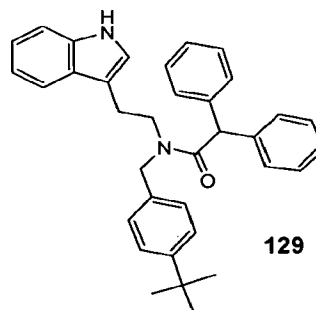
126



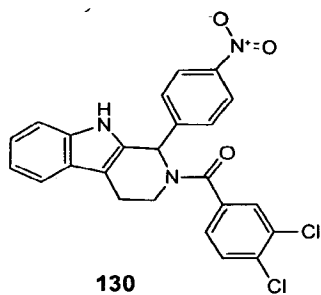
127



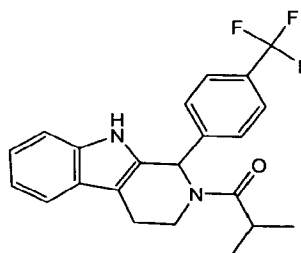
128



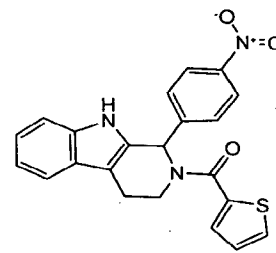
129



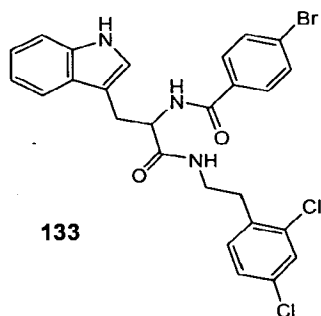
130



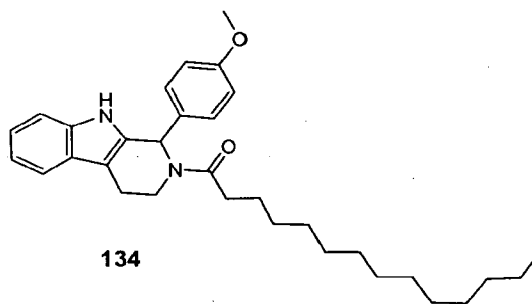
131



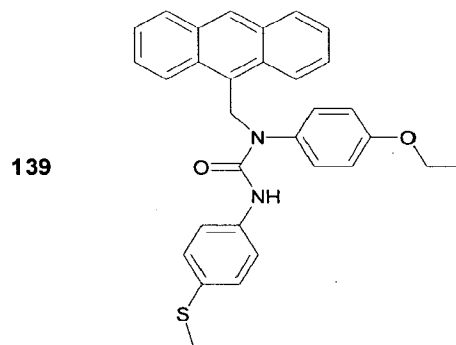
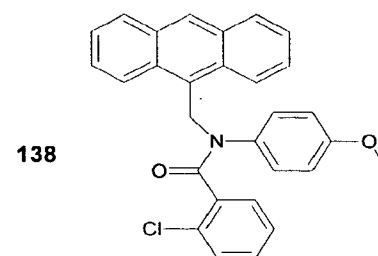
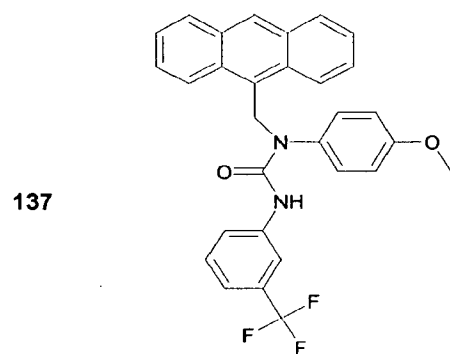
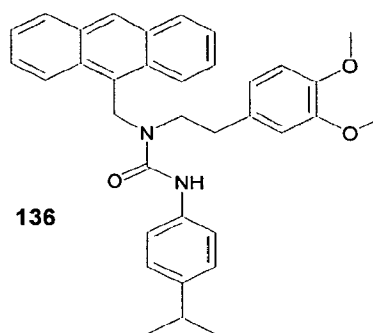
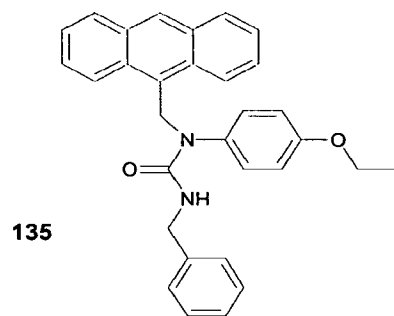
132

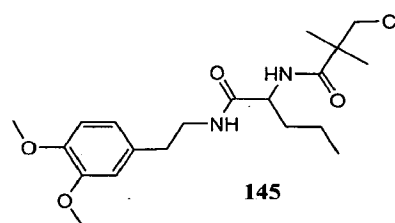
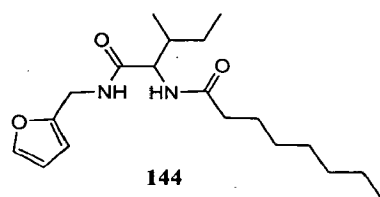
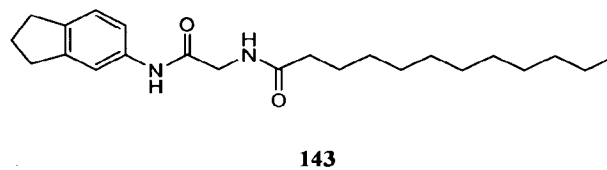
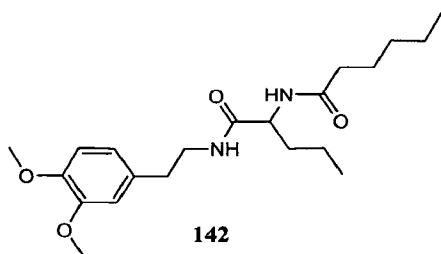
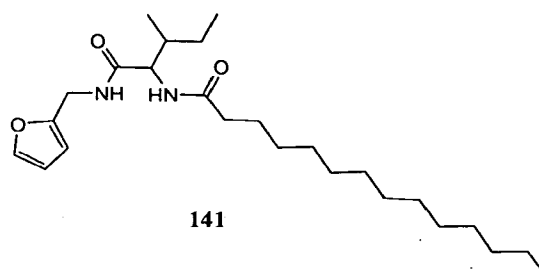
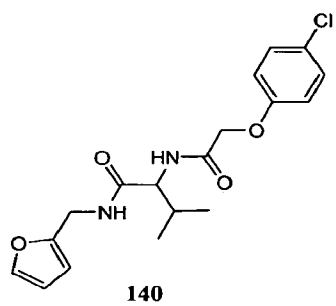


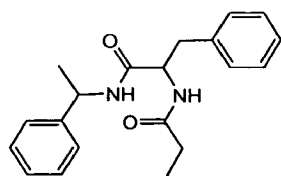
133



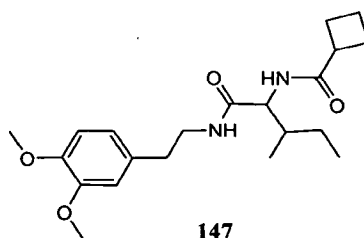
134



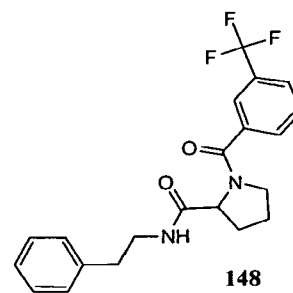




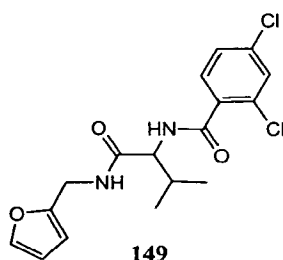
146



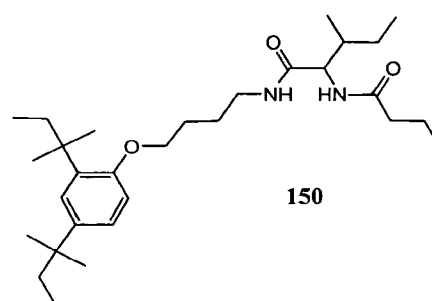
147



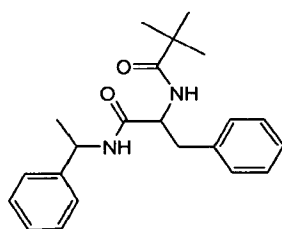
148



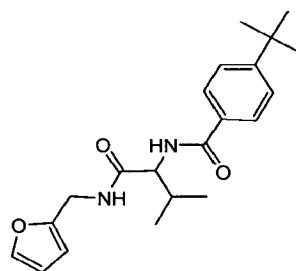
149



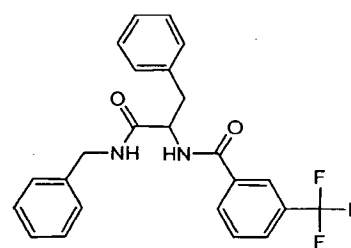
150



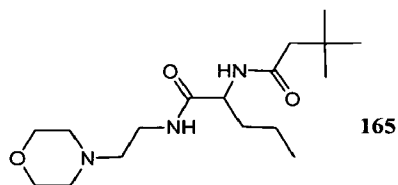
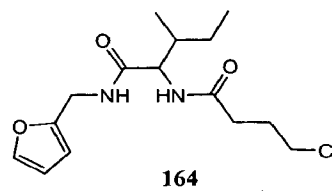
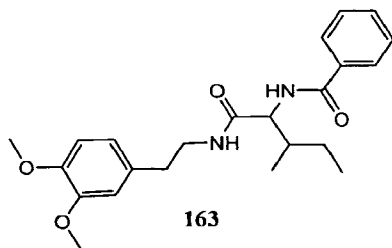
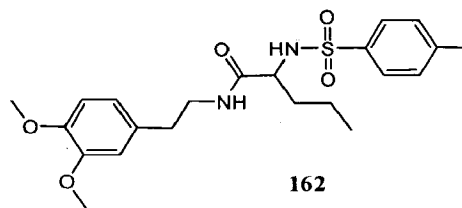
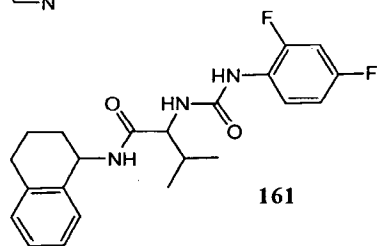
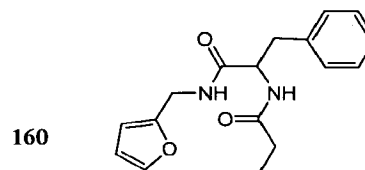
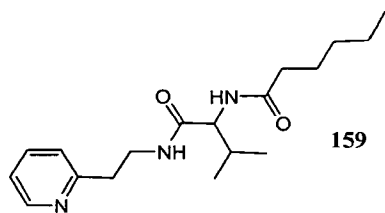
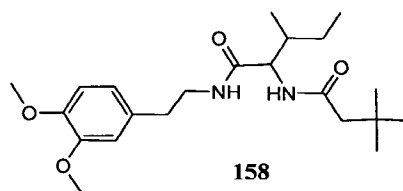
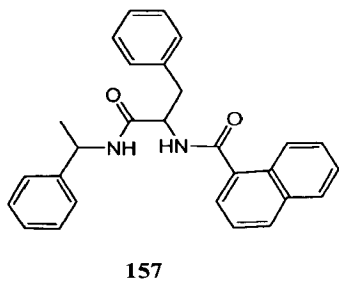
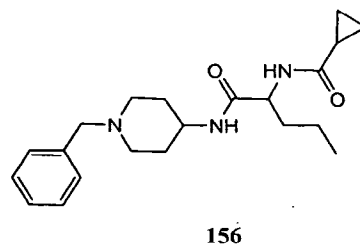
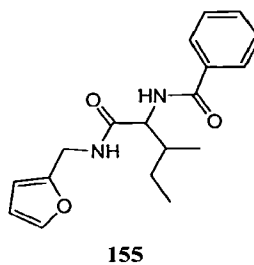
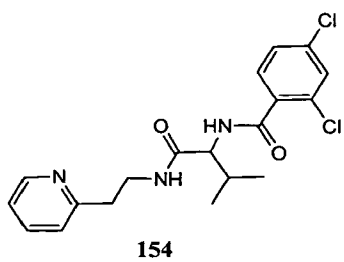
151

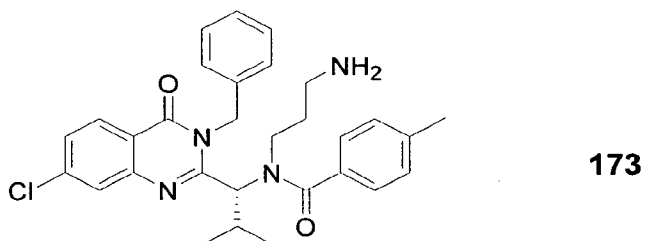
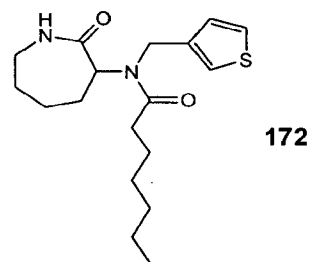
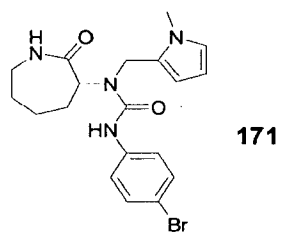
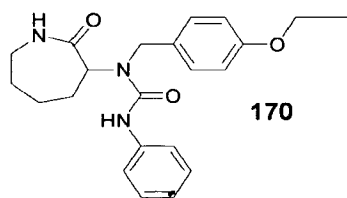
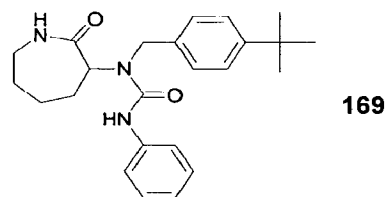
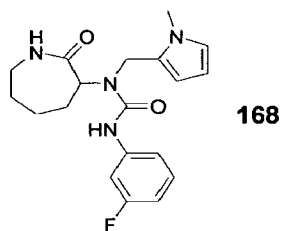
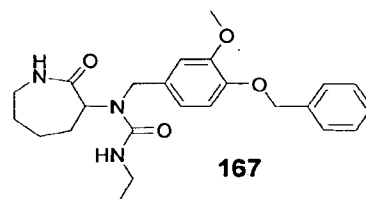
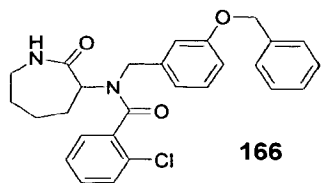


152



153

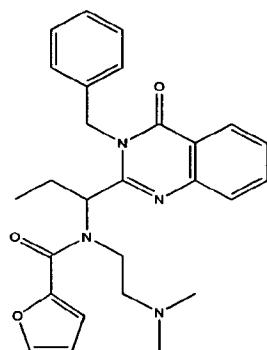




5

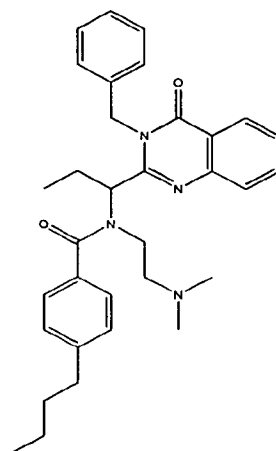
Table 5. Compounds 174 - 183

10

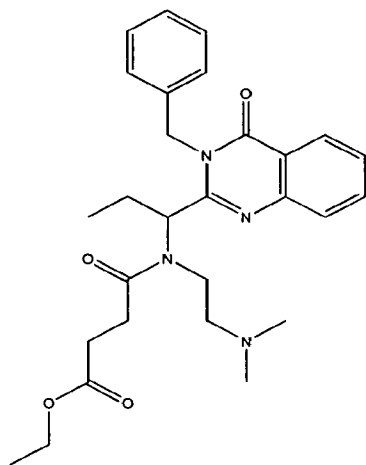


174

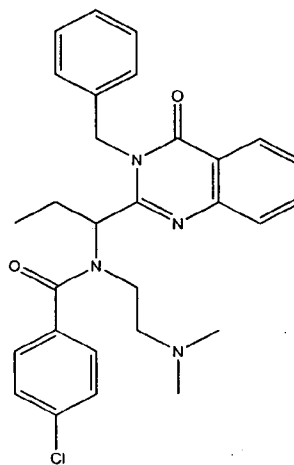
5



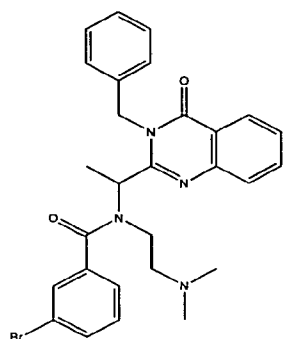
175



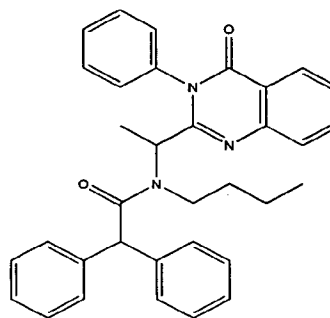
10 176



177

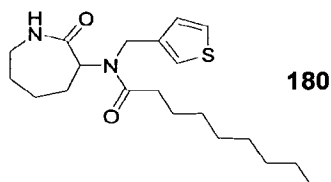


178

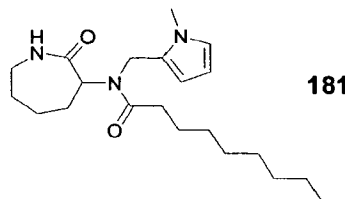


179

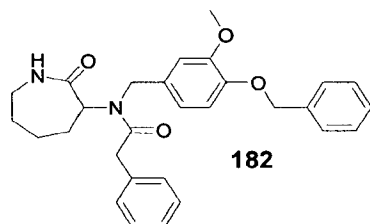
5



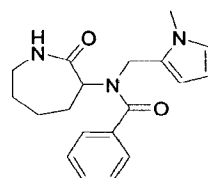
180



181



182



183

10

The following examples are intended to illustrate certain aspects and embodiments of the present invention, but do not exemplify the full scope of the invention.

15 **Examples**

Example 1. A tumor from a patient suspected of having cancer is biopsied. The tissue specimen is assessed using the standard methods known to those skilled in the art to

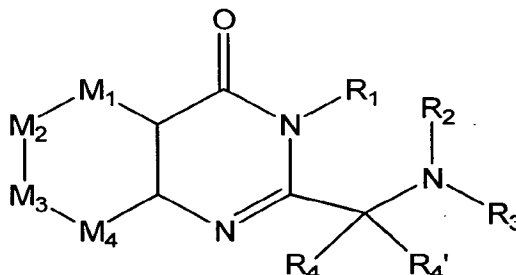
enable an assessment of whether or not the specimen is cancerous. The tissue specimen is then contacted with an antibody raised against the var-PSMGFR peptide (SEQ ID NO: 7). Typically washing and treatment protocols are followed which are familiar to those skilled in the art. A labeled secondary antibody is then used to visualize the areas of antibody reactivity. Alternatively, the primary antibody can be labeled to enable direct detection without the use of a secondary antibody. The presence of the MUC1 receptor in uniform distribution, i.e. not clustered at one point on the cell surface is an indicator to the physician to treat the patient with an agent that inhibits MUC1. Preferred treatments are agents that bind to the MGFR portion of the MUC1 receptor and/or inhibit its cleavage. Especially preferred are compounds disclosed in Tables 2-5, such as Nos. 173 and 96.

While several embodiments of the invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and structures for performing the functions and/or obtaining the results or advantages described herein, and each of such variations or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art would readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that actual parameters, dimensions, materials, and configurations will depend upon specific applications for which the teachings of the present invention are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described. The present invention is directed to each individual feature, system, material and/or method described herein. In addition, any combination of two or more such features, systems, materials and/or methods, if such features, systems, materials and/or methods are not mutually inconsistent, is included within the scope of the present invention.

In the claims (as well as in the specification above), all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” and the like are to be understood to be open-ended, i.e. to mean including but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of” shall be
5 closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, section 2111.03.

What is claimed is:

1. A composition, comprising a structure:



5

wherein M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;

substitutions at positions $M_1 - M_4$ on the above atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon,

10 phosphorous or an atomic null;

R_1 is to be any atom other than halogen;

R_2 and R_3 are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction;

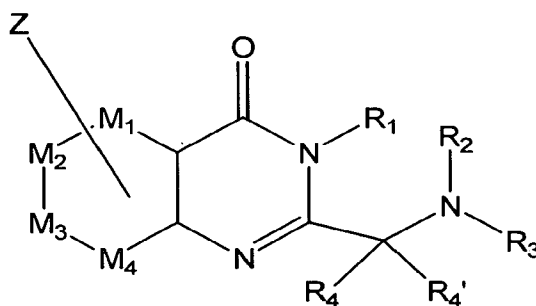
R_2 and R_3 can be covalently linked to give a set of monocyclic *aza*-cycles;

15 R_4 and $R_{4'}$ are independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; and

R_4 and $R_{4'}$ can be covalently linked to give a set of cyclic compounds.

2. A composition, comprising a structure:

20



wherein M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;

5 single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon and nitrogen atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or null;

R_1 is any atom other than halogen;

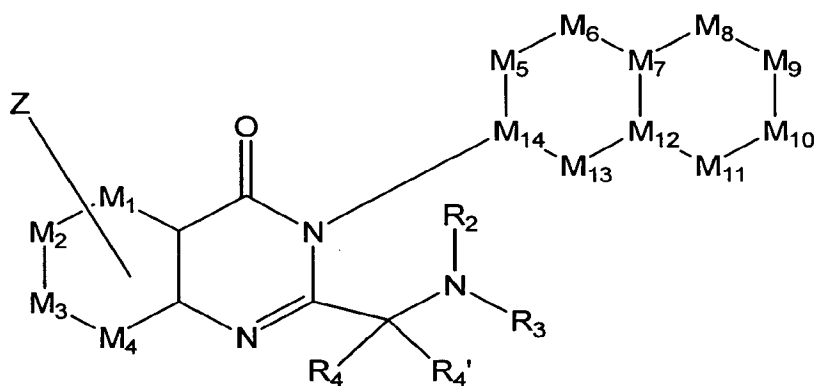
R_2 and R_3 are each independently chosen to be hydrogen, oxygen, carbon,
10 nitrogen or sulfur with other atoms attached; R_2 and R_3 can be covalently linked to give a set of monocyclic *aza*-cycles;

R_4 and $R_{4'}$ are independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; and

R_4 and $R_{4'}$ can be covalently linked to give a set of cyclic compounds.

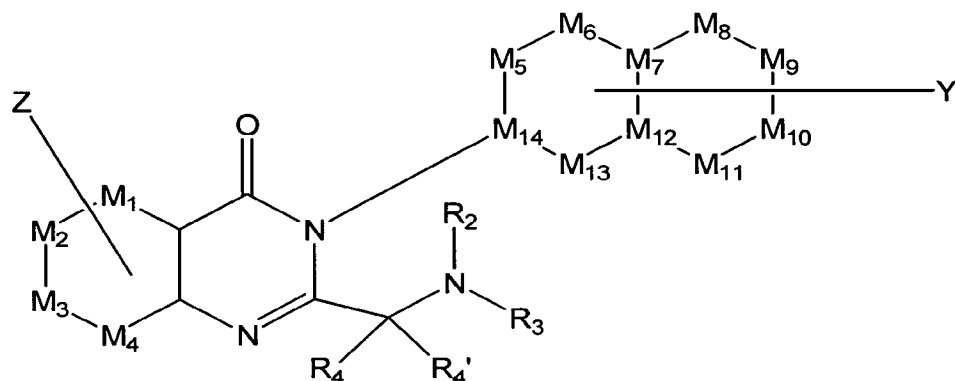
15

3. A composition, comprising a structure:



- wherein M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;
- 5 single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;
- R_1 (M_5-M_{14}) is to be any substituted atom other than hydrogen or halogen and,
- 10 in certain cases, may be either a moiety where M_5 , M_6 , M_7 , M_8 , M_9 , M_{10} , M_{11} , M_{12} , M_{13} and M_{14} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;
- R_2 and R_3 are each independently hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached; R_2 and R_3 may be covalently linked to give a set of
- 15 monocyclic *aza*-cycles;
- R_4 and R_4' are independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions as needed for valance satisfaction; and
- R_4 and R_4' can be covalently linked to give a set of cyclic compounds.

4. A composition, comprising a structure:



5

wherein M₁, M₂, M₃ and M₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;

single and multiple substitutions by atom(s) Z at positions M₁ – M₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls; R₁ (M₅-M₁₄) is any substituted atom other than hydrogen or halogen and, in certain cases, can be either a moiety where M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic nulls;

15

single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

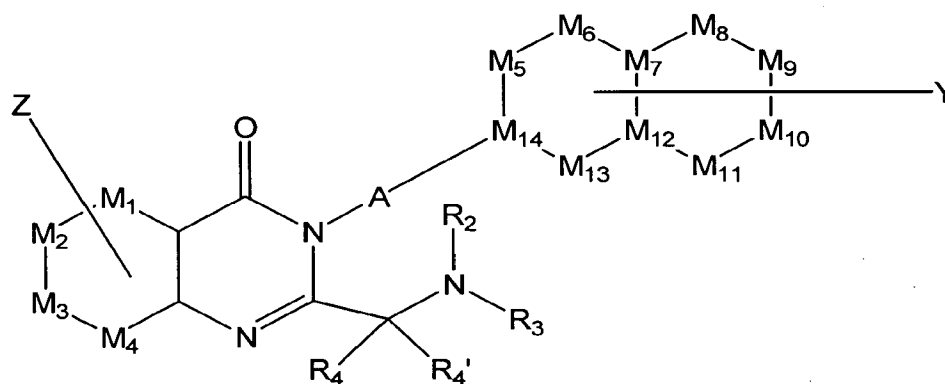
R_2 and R_3 are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction;

R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles;

R_4 and R_4' are independently hydrogen, carbon, oxygen, nitrogen or sulfur with
5 substitutions; and

R_4 and R_4' can be covalently linked to give a set of cyclic compounds.

5. A composition, comprising a structure:



10

wherein M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;

single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the
15 above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

in certain cases, R_1 ($-A-M_5-M_{14}$) is any substituted atom other than hydrogen or halogen and, can be either a moiety where A is chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null;

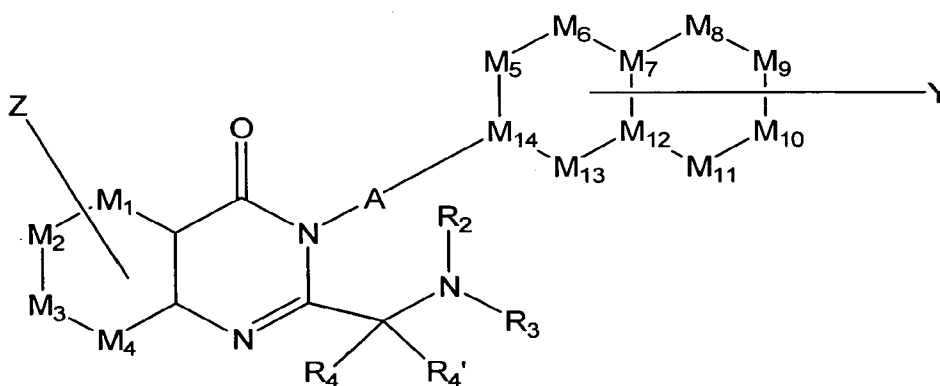
$M_5, M_6, M_7, M_8, M_9, M_{10}, M_{11}, M_{12}, M_{13}$ and M_{14} are each independently
 5 selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null; single and multiple substitutions by atom(s) Y at positions $M_5 - M_{14}$ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls; R_2 and R_3 are each independently chosen to be hydrogen,
 10 oxygen, carbon, nitrogen or sulfur with other atoms attached; R_2 and R_3 can be covalently linked to give a set of monocyclic *aza*-cycles;

R_4 and $R_{4'}$ are independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions; and

R_4 and $R_{4'}$ can be covalently linked to give a set of cyclic compounds.

15

6. A composition, comprising a structure:



wherein M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;

5 single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

 in certain cases, R_1 ($-A-M_5-M_{14}$) is any substituted atom other than hydrogen or
10 halogen and can be either a moiety where A can be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null;

M_5 , M_6 , M_7 , M_8 , M_9 , M_{10} , M_{11} , M_{12} , M_{13} and M_{14} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;

15 single and multiple substitutions by atom(s) Y at positions $M_5 - M_{14}$ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

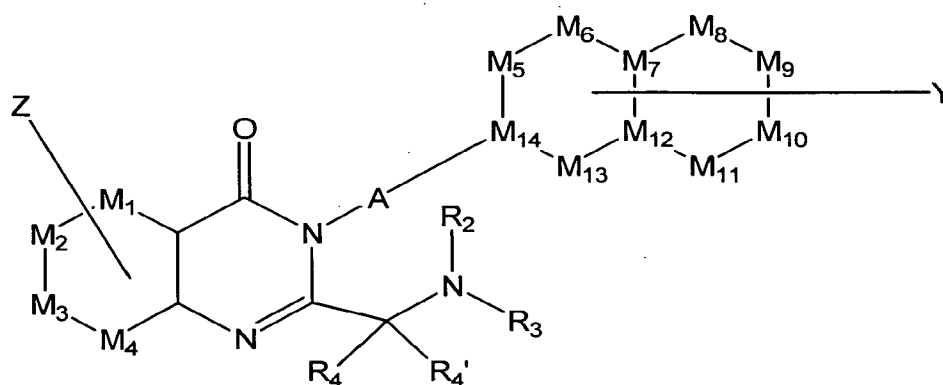
R_2 and R_3 are each independently hydrogen, oxygen, carbon, nitrogen or sulfur
20 with other atoms attached in the latter cases for valance satisfaction; R_2 and R_3 may be covalently linked to give a set of monocyclic *aza*-cycles;

 in certain cases, R_2 is a moiety containing at least one atom other than hydrogen and no more than twenty atoms other than hydrogen;

R_4 and $R_{4'}$ are, independently, hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions; and

R_4 and $R_{4'}$ can be covalently linked to give a set of cyclic compounds.

5 7. A composition, comprising a structure:



wherein M_1 , M_2 , M_3 and M_4 are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;

10 single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

in certain cases, R_1 ($-A-M_5-M_{14}$) is any substituted atom other than hydrogen or
 15 halogen and can be either a moiety where A can be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null;

M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;

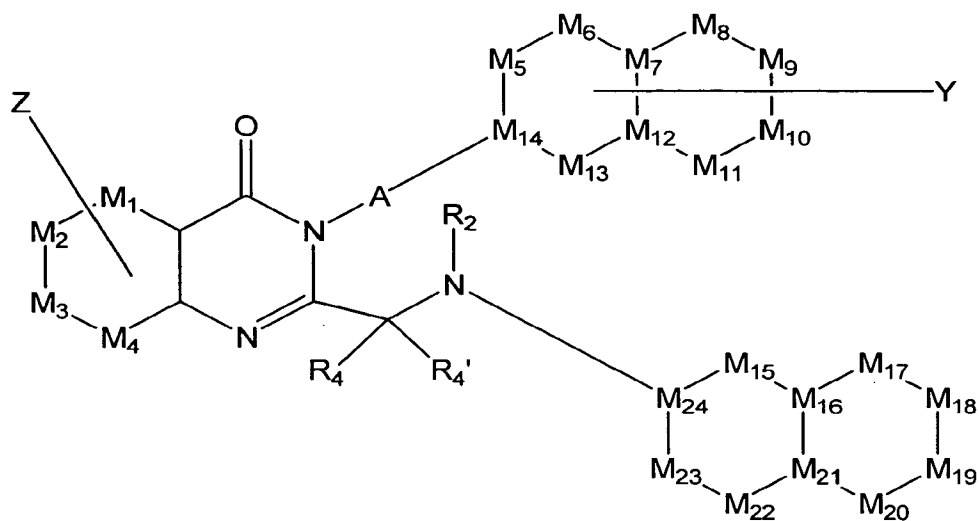
single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the
5 above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

R₂ and R₃ are each independently hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached in the latter cases for valance satisfaction; R₂ and R₃
10 can be covalently linked to give a set of monocyclic *aza*-cycles; in certain cases, R₂ is a moiety containing two atoms other than hydrogen and no more than eight atoms other than hydrogen;

R₄ and R_{4'} are independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions; and

15 R₄ and R_{4'} can be covalently linked to give a set of cyclic compounds.

8. A composition, comprising a structure:



wherein M₁, M₂, M₃ and M₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;

5 single and multiple substitutions by atom(s) Z at positions M₁ – M₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

in certain cases, R₁ (-A-M₅-M₁₄) is any substituted atom other than hydrogen or halogen and can be either a moiety where A can be chosen from the set of substituted
10 carbon, nitrogen, sulfur, oxygen or an atomic null;

M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;

15 single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the above designated carbon, nitrogen and sulfur atoms may be hydrogen or halogen, or

substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls; R_2 and R_3 are each independently hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached; R_2 and R_3 can be covalently linked to give a set of monocyclic *aza*-cycles;

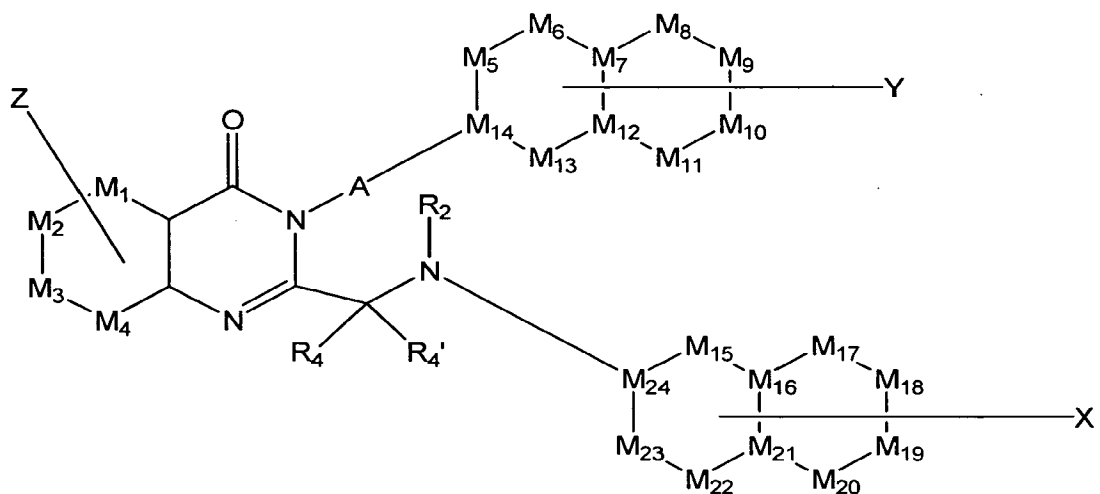
- 5 in certain cases, R_2 is a moiety containing two atoms other than hydrogen and no more than eight atoms other than hydrogen;

R_3 (M_{15} - M_{24}) is any substituted atom other than hydrogen or halogen and, in certain cases, can be either a moiety where M_{15} , M_{16} , M_{17} , M_{18} , M_{19} , M_{20} , M_{21} , M_{22} , M_{23} and M_{24} are each independently selected from the group consisting of substituted
10 carbon, nitrogen, sulfur, oxygen and/or an atomic null;

R_4 and R_4' are independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions; and

R_4 and R_4' can be covalently linked to give a set of cyclic compounds.

- 15 9. A composition, comprising a structure:



wherein M₁, M₂, M₃ and M₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;

5 single and multiple substitutions by atom(s) Z at positions M₁ – M₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls; in certain cases, R₁ (-A-M₅-M₁₄) is any substituted atom other than hydrogen or halogen and can be either a moiety where A can be chosen from the set of
10 substituted carbon, nitrogen, sulfur, oxygen or an atomic null;

M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null; single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or
15 halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

R₂ and R₃ are each independently chosen to be hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached; R₂ and R₃ can be covalently linked to give a set of monocyclic *aza*-cycles;

in certain cases, R₂ is a moiety containing two atoms other than hydrogen and
5 no more than eight atoms other than hydrogen;

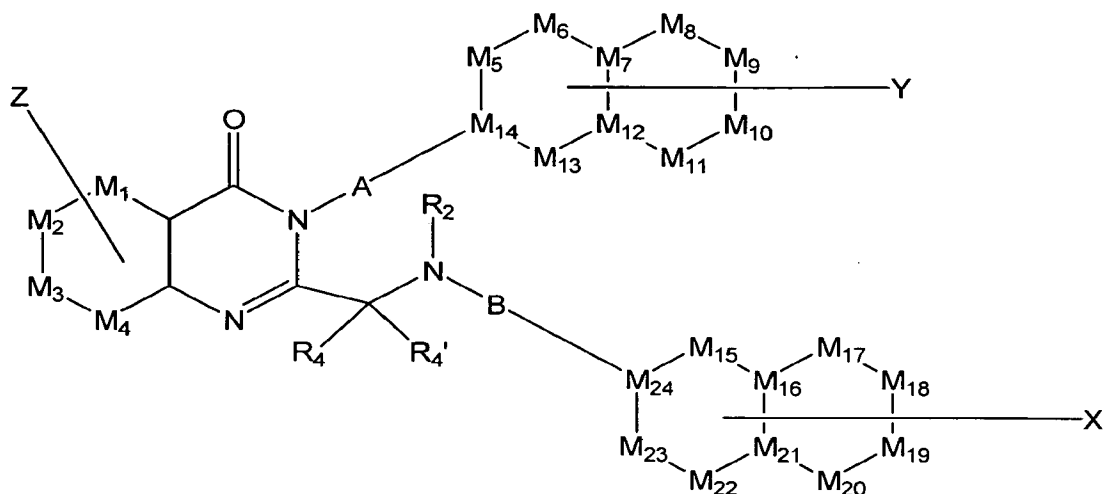
R₃ (M₁₅-M₂₄) is any substituted atom other than hydrogen or halogen and, in certain cases, can be either a moiety where M₁₅, M₁₆, M₁₇, M₁₈, M₁₉, M₂₀, M₂₁, M₂₂, M₂₃ and M₂₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;

10 single and multiple substitutions by atom(s) X at positions M₁₅ – M₂₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

R₄ and R_{4'} are independently hydrogen, carbon, oxygen, nitrogen or sulfur with
15 substitutions; and

R₄ and R_{4'} can be covalently linked to give a set of cyclic compounds.

10. A composition, comprising a structure:



wherein M₁, M₂, M₃ and M₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;

5 single and multiple substitutions by atom(s) Z at positions M₁ – M₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

10 in certain cases, R₁ (-A-M₅-M₁₄) is any substituted atom other than hydrogen or halogen and can be either a moiety where A can be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null;

15 M₅, M₆, M₇, M₈, M₉, M₁₀, M₁₁, M₁₂, M₁₃ and M₁₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null; single and multiple substitutions by atom(s) Y at positions M₅ – M₁₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

R₂ and R₃ are each independently hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached; R₂ and R₃ can be covalently linked to give a set of monocyclic *aza*-cycles;

in certain cases, R₂ is a moiety containing two atoms other than hydrogen and
5 no more than eight atoms other than hydrogen;

in certain cases, R₃ (-B-M₁₅-M₂₄) is any substituted atom other than hydrogen or halogen and, can be either a moiety where B, a linker, may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null;

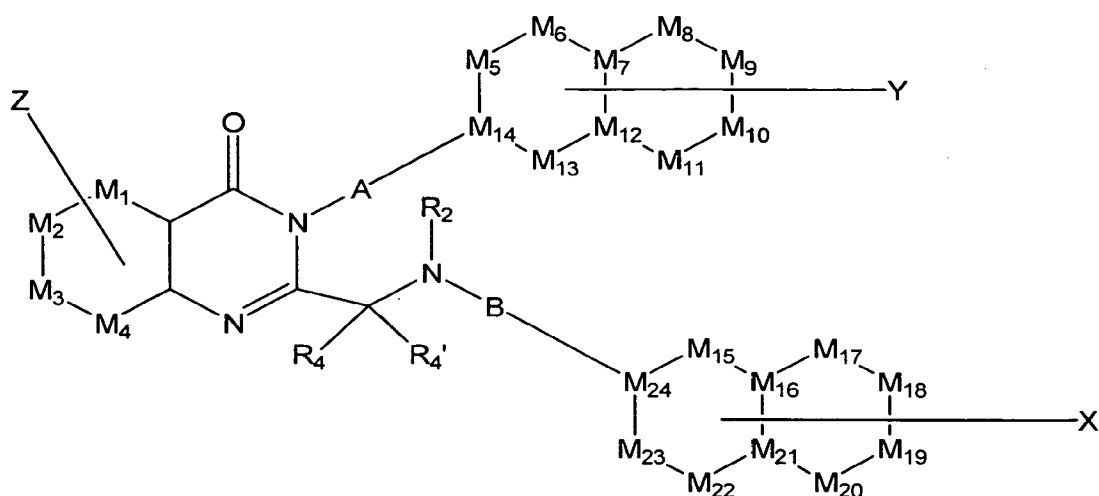
B can be chosen as an atomic null through an octa-atomic set of non-hydrogen
10 atoms; M₁₅, M₁₆, M₁₇, M₁₈, M₁₉, M₂₀, M₂₁, M₂₂, M₂₃ and M₂₄ are any substituted atom other than hydrogen or halogen, and in certain cases, can be either a moiety where M₁₅, M₁₆, M₁₇, M₁₈, M₁₉, M₂₀, M₂₁, M₂₂, M₂₃ and M₂₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;

15 single and multiple substitutions by atom(s) X at positions M₁₅ – M₂₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

R₄ and R_{4'} are, independently, hydrogen, carbon, oxygen, nitrogen or sulfur with
20 substitutions; and

R₄ and R_{4'} can be covalently linked to give a set of cyclic compounds.

11. A composition, comprising a structure:



- wherein M_1 , M_2 , M_3 and M_4 are each independently selected from the group
- 5 consisting of substituted carbon, nitrogen, sulfur, oxygen, and/or an atomic null;
- single and multiple substitutions by atom(s) Z at positions $M_1 - M_4$ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;
- 10 in certain cases, R_1 ($-A-M_5-M_{14}$) is any substituted atom other than hydrogen or halogen and can be either a moiety where A may be chosen from the set of substituted carbon, nitrogen, sulfur, oxygen or an atomic null;
- M_5 , M_6 , M_7 , M_8 , M_9 , M_{10} , M_{11} , M_{12} , M_{13} and M_{14} are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen
- 15 and/or an atomic null; single and multiple substitutions by atom(s) Y at positions $M_5 - M_{14}$ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or

halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or atomic nulls;

R₂ and R₃ are each independently hydrogen, oxygen, carbon, nitrogen or sulfur with other atoms attached; R₂ and R₃ can be covalently linked to give a set of

5 monocyclic *aza*-cycles;

in certain cases, R₂ is a moiety containing two atoms other than hydrogen and no more than eight atoms other than hydrogen;

in certain cases, R₃ (-B-M₁₅-M₂₄) is any substituted atom other than hydrogen or halogen and can be either a moiety where B, a linker, can be chosen from the set of
10 substituted carbon, nitrogen, sulfur, oxygen or an atomic null;

B can be chosen as an atomic null through an octa-atomic set of non-hydrogen atoms; M₁₅, M₁₆, M₁₇, M₁₈, M₁₉, M₂₀, M₂₁, M₂₂, M₂₃ and M₂₄ are to be any substituted atom other than hydrogen or halogen;

in certain cases, B can be either a moiety where M₁₅, M₁₆, M₁₇, M₁₈, M₁₉, M₂₀,
15 M₂₁, M₂₂, M₂₃ and M₂₄ are each independently selected from the group consisting of substituted carbon, nitrogen, sulfur, oxygen and/or an atomic null;

single and multiple substitutions by atom(s) X at positions M₁₅ – M₂₄ on the above designated carbon, nitrogen and sulfur atoms can be hydrogen or halogen, or substituted carbon, nitrogen, oxygen, sulfur, boron, selenium, silicon, phosphorous or
20 atomic nulls;

R₄ and R_{4'} are independently hydrogen, carbon, oxygen, nitrogen or sulfur with substitutions;

R₄ and R_{4'} can be covalently linked to give a set of cyclic compounds; and

in certain cases, R_4 and R_4 comprise from one to twenty atoms.

12. A method for the treatment or prevention of MUC1-positive cancers comprising acts of:

- 5 testing a sample derived from a patient; and
 determining an aberrant expression of MUC1; then
 treating the patient with at least one composition from Table 2, 3, 4 or 5.

13 A method for the treatment or prevention of MUC1-positive cancers comprising
10 acts of:

- testing a sample derived from a patient; and
 determining an aberrant expression of MUC1; then
 treating the patient with composition no. 173

14. A method for the treatment or prevention of MUC1-positive cancers comprising
15 acts of:

- testing a sample derived from a patient; and
 determining the aberrant expression of MUC1;
 then treating the patient with composition no. 96.

20 15. A method for the treatment or prevention of MUC1-positive cancers comprising
 an act of:

- inhibiting cleavage of MUC1 by treating the patient with Composition No. 173.

25 16. A method for the treatment or prevention of MUC1-positive cancers comprising
 an act of:

- inhibiting cleavage of MUC1 by treating the patient with Composition No. 96

17. A method comprising acts of:
30 administering to a patient a composition as in any one of claims 1 – 11; and

treating or preventing via the administration a cancer that is characterized by the aberrant expression of MUC1.

18 A method comprising acts of:

5 administering to a patient any single composition or combination of compositions from Tables 2, 3, 4, or 5; and

treating or preventing via the administration a cancer that is characterized by the aberrant expression of MUC1.

10 19. A method comprising acts of:

administering to a patient a composition as recited in any one of Claims 1 – 11;

and

treating or preventing via the administration a proliferative disease that is characterized by the aberrant expression of a hedgehog protein.

15

20 A method comprising acts of:

administering to a patient any single composition or combination of compositions from Tables 2, 3, 4, or 5; and

20 treating or preventing via the administration a cancer that is characterized by the aberrant expression of a hedgehog protein.

21. A method as in Claim 12 or 13, wherein aberrant expression of MUC1 involves a loss of the clustering pattern of MUC1 expression.

25 22. A method as in Claim 12 or 13, wherein aberrant expression of MUC1 involves an increase in the cleavage of MUC1.

23. A method as in Claim 12 or 13, wherein aberrant expression of MUC1 involves cleavage of MUC1 that releases at least a portion of the IBR.

30

24. A method for the treatment or prevention of cancer, comprising an act of:

administering to a patient an agent that is able to chelate a metal, wherein the metal is chosen from the group zinc, magnesium, and nickel.

25. A method as in Claim 24, wherein the agent inhibits a metal-dependent protein.
- 5
26. A method as in Claim 25, wherein the metal dependent protein is a member of the kinesin family
27. A method as in Claim 26, wherein the metal dependent protein is kinesin spindle protein.
- 10
28. A method as in Claim 26, wherein the metal dependent protein is Costal2.
29. A method as in Claim 26, wherein the metal dependent protein is from the hedgehog family.
- 15
30. A method as in Claim 25, wherein the metal dependent protein is an enzyme that affects MUC1 cleavage.
- 20
31. A method as in Claim 30, wherein the enzyme is a matrix metalloprotease.
32. A method as in Claim 31, wherein the enzyme is MT1-MMP.
33. A method as in Claim 30, wherein the enzyme is Furin.
- 25
34. A method as in Claim 30, wherein the enzyme is ADAM-17-TASE.
35. A method for the treatment or prevention of MUC1 associated cancer comprising an act of:
- 30 administering an agent that inhibits the cleavage of MUC1.

36. A method as in Claim 35, wherein the agent is a TIMP.
37. A method as in Claim 36, wherein the agent is TIMP 2.
- 5 38. A method as in Claim 36, wherein the agent is TIMP 3.
39. A method for the treatment or prevention of cancer comprising an act of:
administering to a patient an agent that binds to the MGFR portion of MUC1
and also contains a metal chelate moiety,
10 wherein the moiety is able to chelate at least one of the metals selected from the
group consisting of: zinc, magnesium, and nickel.
40. A method for the treatment or prevention of cancers that comprise cells that
bear cell surface receptors that shuttle from the surface to the interior of the cell
15 (receptor shuttling), comprising an act of:
administering to a patient an agent that has a first functionality that allows it to
bind to a cell surface receptor and a second functionality that acts on an intracellular
element that is involved in the progression of cancer, the agent being delivered to the
intracellular components by the mechanism of receptor shuttling.
20
41. A method as in Claim 40, wherein the receptor is MUC1.
42. A method as in Claim 41, wherein the agent is Compound No. 173.
- 25 43. A method as in Claim 41, wherein the agent is Compound No. 96.
44. A method comprising an act of:
affecting the signaling of receptors that span the membrane several times via
administering an agent that chelates a metal.
30
45. A method as in Claim 44, wherein the metal is zinc.

46. A method as in Claim 44, wherein the agent is Compound No. 84.

APPLICATION DATA SHEET FORM

Inventor Information

Inventor One Given Name::	Cynthia C.
Family Name::	Bamdad
Postal Address Line One::	356 Marlborough Street, #2
City::	Boston
State or Province::	MA
Country::	United States
Postal or Zip Code::	02116
City of Residence::	Boston
State or Province of Residence::	MA
Country of Residence::	United States
Citizenship Country::	United States

Correspondence Information

Name Line One::	Timothy J. Oyer, Ph.D.
Name Line Two::	Wolf, Greenfield & Sacks, P.C.
Address Line One:	600 Atlantic Avenue
City::	Boston
State or Province::	MA
Country::	U.S.A.
Postal or Zip Code::	02210-2206
Telephone One::	(617) 646-8000
Telephone Two::	(617) 646-8251
Fax Number:	(617) 646-8646
Electronic Mail::	toyer@wolfgreenfield.com

Application Information

Title Line One::	TECHNIQUES FOR DIAGNOSIS AND TREATMENT
Title Line Two::	OF CANCER (MUC 1)
Total Drawing Sheets::	None
Formal Drawings?::	None
Claims::	46
Application Type::	Provisional
Docket Number::	M1015.70090US00
Licensed US Govt. Agency::	
Contract or Grant Numbers One::	
Contract or Grant Numbers Two::	
Secrecy Order in Patent Appl.?::	

Application Data Sheet Form

Representative Information

Representative Customer Number:: 23628

Continuity Information N/A

Prior Foreign Applications N/A

Assignee Information:

Assignee name:: Minerva Biotechnologies Corporation
Street of mailing address:: 6th Floor Rosentiel Bldg., M/S 029
15 South Street
City of mailing address:: Waltham
State or Province of mailing address:: MA
Postal or Zip Code of mailing address:: 02454-9110

NOTE: *If there is more than one assignee, this information should be repeated for each one.*

NOTE: *Assignment information provided on an ADS will not be officially recorded for this application. Assignment Information is considered recorded when submitted as provided in Title 37, Section 3. Assignment information submitted on an ADS only results in the assignment information being included on the patent application publication.*